Journal of the American College of Cardiology Vol. 61, No. 3, 2013

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.12.002

HIGHLIGHTS FROM *JACC*

Highlights of the Year in *JACC* 2012

Anthony N. DeMaria, MD,* Jeroen J. Bax, MD, PhD,† Gregory K. Feld, MD,*
Barry H. Greenberg, MD,* Jennifer L. Hall, PhD,‡ Mark A. Hlatky, MD,§ Wilbur Y. W. Lew, MD,‖
João A. C. Lima, MD,¶ Ehtisham Mahmud, MD,* Alan S. Maisel, MD,‖
Sanjiv M. Narayan, MD, PhD,‖ Steven E. Nissen, MD,# David J. Sahn, MD,** Sotirios Tsimikas, MD*

San Diego and Stanford, California; Leiden, the Netherlands; Minneapolis, Minnesota; Baltimore, Maryland; Cleveland, Ohio; and Portland, Oregon

As in past years, this Highlights article takes the place of the Editor's Page, and was assembled by the associate editors based upon the papers that they perceived had or would have the greatest impact upon cardiology. Space constraints result in omitting many excellent papers, and we apologize in advance to those authors.

Transcatheter aortic valve replacement. Perhaps the most exciting advance this past year involved the development, validation, and approval of transcatheter aortic valve replacement (TAVR) for aortic stenosis.

A weighted meta-analysis of 16 studies including 3,519 patients determined the rates of major outcomes after TAVR using Valve Academic Research Consortium (VARC) definitions and demonstrated a high adverse event rate at present. Device success was 92.1%, all-cause 30-day mortality 7.8%, myocardial infarction (MI) 1.1%, acute kidney injury stage II/III 7.5%, life-threatening bleeding 15.6%, major vascular complications 11.9%, major stroke 3.2%, and new permanent pacemaker implantation 13.9%. Medtronic CoreValve (Minneapolis, Minnesota) prosthesis use was associated with a significant higher rate of new permanent pacemaker implantation compared with the Edwards Lifesciences prosthesis (28.9% vs. 4.9%, $p < 0.0001$). The 30-day safety composite endpoint rate was 32.7%, and the 1-year total mortality rate was 22.1% (1).

The severity of periprosthetic aortic regurgitation (periAR) was prospectively evaluated in 146 patients treated with the Medtronic CoreValve prosthesis by echo, angiography, and measurement of the aortic regurgitation (AR) index = [(diastolic blood pressure − left ventricular end-diastolic pressure)/systolic blood pressure × 100] (2). The AR index decreased stepwise from 31.7 with no periAR to 28.0 with mild, 19.6 with moderate, and 7.6 with severe periAR ($p < 0.001$). Patients with an AR index <25 had a significantly increased 1-year mortality risk. The AR index provided additional prognostic information beyond the echocardiographically assessed severity of periAR and independently predicted 1-year mortality (hazard ratio [HR]: 2.9; $p = 0.009$).

A total of 202 consecutive patients with no baseline ventricular conduction disturbances who underwent balloon-expandable valve TAVR were examined to assess new left bundle branch block (LBBB). New-onset LBBB was observed in 30% of patients after TAVR, and had resolved in 37.7% and 57.3% at hospital discharge and 6- to 12-month follow-up, respectively. Baseline QRS duration and ventricular depth of the prosthesis were independent predictors of persistent LBBB, which was associated with decreased ejection fraction at hospital discharge and poorer functional status at 1 year. Patients with persistent LBBB and no pacemaker at hospital discharge had more syncope (16.0% vs. 0.7%; $p < 0.001$) and greater permanent pacemaker need (20.0% vs. 0.7%; $p < 0.001$), but not global mortality. Up to 30% of patients with no prior conduction disturbances developed new LBBB following TAVR with a balloon expandable valve, although it was transient in more than one-third (3).

A total of 358 patients underwent transapical TAVR with balloon-expandable prostheses using a modified procedural strategy of precise prosthesis positioning and immediate additional intraprocedural treatment with the goal to eliminate paravalvular leakage (4). Balloon redilation of the transcatheter valve was performed in 18 patients (5%), and additional second valves were implanted in 13 (4%). At the end of the procedure, 52% had no paravalvular or transvalvular regurgitation. Leakage was trace in 25%, mild in 23%, and moderate in 6% of patients. Cumulative survival was not dependent on post-procedural regurgitation rate.

Consecutive patients (n = 137) undergoing transfemoral TAVR from 2009 to 2010 were evaluated at baseline, post-procedure, and at 30 days (5). Smaller sheaths, rigorous angiographic and computed tomographic screening and

From the *Cardiology Division, UCSD Medical Center, San Diego, California; †Leiden University Medical Center, Leiden, the Netherlands; ‡University of Minnesota, Minneapolis, Minnesota; §Stanford University, Stanford, California; ‖Veterans Affairs Medical Center, San Diego, California; ¶Johns Hopkins Hospital, Baltimore, Maryland; #Department of Cardiology, Cleveland Clinic, Cleveland, Ohio; and the **Pediatric Cardiology, Oregon Health and Science University, Portland, Oregon. All relationships with industry information for each author are available online on the *JACC* home page.

JACC Vol. 61, No. 3, 2013
January 22, 2013:357–85

patient selection, and percutaneous vascular repair techniques were increasingly used over this period. Over the 2 years, major vascular complications decreased from 8% to 1% ($p = 0.06$), minor vascular complications decreased from 24% to 8% ($p < 0.01$), major bleeds fell from 14% to 1% ($p < 0.01$), and unplanned surgery decreased from 28% to 2% ($p < 0.01$). A smaller artery than sheath diameter, moderate or severe calcification, and peripheral vascular disease were associated with higher vascular complication rates.

The outcomes of patients with mitral regurgitation (MR) were evaluated after TAVR (6). Moderate or severe MR in patients undergoing TAVR is associated with a higher early, but not late, mortality rate. One year after TAVR, moderate MR had improved in 58% of patients, remained moderate in 17%, and worsened to severe in 1%, and 24% of patients had died. Severe MR had improved in 49% and remained severe in 16%, and 35% of patients had died. Improvement was more likely in patients with high transaortic gradients, with functional MR, without pulmonary hypertension and without atrial fibrillation. Two studies from Europe and Canada reported that female sex is associated with better short- and long-term survival after TAVR (7,8).

The most definitive studies regarding TAVR in high-risk or inoperable patients were the PARTNER trials (Placement of AoRTic TraNscathetER Valve Trial) (9). In a substudy of PARTNER, Reynolds et al. (10) reported the health-related quality of life after TAVR in high-risk patients with severe aortic stenosis (AS). The primary outcome, the Kansas City Cardiomyopathy Questionnaire summary score, improved more rapidly with TAVR but was similar for the 2 groups at 6 and 12 months. However, there was significant interaction between the benefit of TAVR and access site; patients undergoing transfemoral TAVR demonstrated significant improvement in health status. In another substudy, Genereux et al. (11) report on vascular complications after TAVR. They observed that 15.3% of patients had major and 11.9% minor vascular complications within 30 days of the procedure, most frequently vascular dissection, perforation, and access site hematoma. Major complications were associated with a significantly higher 30-day rate of major bleeding, transfusions, renal failure requiring dialysis, and a higher 30-day and 1-year mortality. The only identifiable independent predictor of complications was female sex.

In an attempt to standardize definitions and endpoints of clinical studies involving TAVR, the VARC updated their second consensus document in *JACC* (12). The VARC documents have provided the mainstay of standardization for designing and reporting clinical trials of TAVR in patients with critical AS.

Which measurement to use for aortic annular sizing before transcatheter aortic valve implantation remains unclear. Using 4-dimensional analysis of 256-slice computed tomography (CT), it was shown that the aortic annulus assumes a more round shape in systole, which increases the cross-sectional area without changing the perimeter in patients with calcified aortic valves. Accordingly, the annulus perimeter may be the preferred measurement for sizing in transcatheter aortic valve implantation (13).

Several studies have examined the optimal imaging technique to measure aortic annulus size so as to limit the risk of aortic regurgitation. Jilaihawi et al. (14) compared computed tomography to 2-dimensional echocardiography and found the computed tomography superior in sizing the aortic annulus for TAVR procedures, and reduced the occurrence of aortic regurgitation worse than mild from 21.9% to 7.5% compared with 2-dimensional echo. Willson et al. (15) found similar results despite the use of 3-dimensional echocardiography; the difference between the size of the valve and of the aortic annulus by computed tomography was predictive of the presence of aortic regurgitation. These 2 papers together clearly establish the superiority of computed tomography in assessing aortic annulus and preventing aortic regurgitation in TAVR. Finally, the incidence and predictive factors for atrial fibrillation following TAVR were reported by Amat-Santos et al. (16). They found that new-onset atrial fibrillation occurred in 31.9% of patients at a median of 48 h after the procedure, and were predicted by a left atrial size and the transapical approach. At 30 days, atrial fibrillation was associated with a higher rate of stroke and systemic embolus (13.6 vs. 3.2) with no difference in mortality rate.

STENT trials. The TWENTE trial (The Real-World Endeavor Resolute Versus XIENCE V Drug-Eluting SteNt Study: Head-to-head Comparison of Clinical Outcome After Implantation of Second Generation Drug-eluting Stents in a Real World Scenario) compared the safety and efficacy of Resolute (Medtronic) zotarolimus-eluting stents (ZES) ($n = 699$) with Xience V (Boston Scientific, Natick, Massachusetts) everolimus-eluting stents (EES) ($n = 694$) at 1 year (9). Acute coronary syndromes were present in 52% and "off-label" features in 77% of patients. In ZES and EES, target vessel baseline occurred in 8.2% and 8.1%, respectively (absolute risk-difference 0.1%; p-noninferiority = 0.001). Resolute ZES were noninferior to Xience V EES in treating "real-world" patients with a vast majority of complex lesions and "off-label" indications for drug-eluting stents (17).

The SORT OUT IV (Scandinavian Organization for Randomized Trials With Clinical Outcome IV) trial compared 1,390 patients treated with EES or sirolimus-eluting stents (SES) (18). At 2 years, the composite primary endpoint occurred in 8.3% in the EES group and in 8.7% in the SES group (HR: 0.94). Rate of definite stent thrombosis was lower in the EES group (0.2% vs. 0.9%) EES was noninferior to the SES for both patient-related and stent-related clinical outcomes.

Patients with in-stent restenosis of DES were randomized according to lesion length to compare outcomes of SES versus cutting balloon angioplasty for focal type ($\leq$10 mm, $n = 96$) and SES versus EES for diffuse type (>10 mm, $n = 66$) (19). In focal lesions, in-segment late loss was

significantly higher in the cutting balloon group than in the SES group (0.25 mm vs. 0.06 mm). In diffuse in-stent restenosis, in-segment late loss (0.11 mm vs. 0.00 mm), in-segment restenosis rate (5.0% vs. 14.3%), and the composite of death, MI, or target vessel restenosis [TVR] (9.6% vs. 8.8%) did not differ between SES and EES. For focal DES restenosis, repeat SES implantation is more effective than cutting balloon angioplasty. For diffuse DES restenosis, implantation of SES or EES is comparably effective.

Patients (n = 2,095) treated with placlitaxel-coated balloons (PCB) were evaluated for clinically driven target lesion revascularization (TLR) rate at 9 months in 75 centers (20). The TLR rate was 5.2% after 9.4 months, and definite vessel thrombosis occurred in 0.1%. PCB angioplasty was more effective in bare-metal stent (BMS) restenosis compared with DES restenosis, with no difference regarding the type of DES. PCB angioplasty in an all-comers, prospective, multicenter registry was safe, and confirmed in a large population the low TLR rates seen in randomized clinical trials.

This PEPCAD DES (Treatment of DES-In-Stent Restenosis With SeQuent Please Paclitaxel Eluting PTCA Catheter) study (21), was a prospective, single-blind, multicenter trial that randomly assigned 110 patients to PCB angioplasty for treatment of DES restenosis compared with uncoated balloon angioplasty. Treatment with PCB was superior to balloon angioplasty alone, with a late loss of 0.43 mm versus 1.03 mm ($p < 0.001$). Restenosis rate was significantly reduced from 58.1% to 17.2% ($p < 0.001$), and the composite clinical endpoint was significantly reduced from 50.0% to 16.7% ($p < 0.001$), respectively. The DEB-AMI (Drug-Eluting Balloon in Acute MI) study (22) compared PCB plus BMS versus BMS versus DES for acute ST-segment elevation MI (STEMI). In contrast to the aforementioned studies, PCB in STEMI patients followed by BMS implantation failed to show angiographic superiority to BMS only. Angiographic results of DES were superior to both BMS and DEB. Moreover, PCB before implantation induced more uncovered and malapposed stent struts than BMS, but fewer than after.

The EVOLVE (A Prospective Randomized Multicenter Single-Blind Noninferiority Trial to Assess the Safety and Performance of the Evolution Everolimus-Eluting Monorail Coronary Stent System for the Treatment of a De Novo Atherosclerotic Lesions) study (23) compared the safety and efficacy of a novel bioabsorbable polymer EES (SYNERGY) with that of the durable polymer PROMUS Element EES (n = 291) (both stents, Boston Scientific). Patients were randomly assigned in a 1:1:1 ratio to PROMUS Element, SYNERGY, or SYNERGY half-dose. The 30-day primary clinical endpoint of target lesion failure occurred in 0%, 1.1%, and 3.1% of patients in the PROMUS Element, SYNERGY, and SYNERGY half-dose groups, respectively. The 6-month in-stent late loss was 0.15 mm for PROMUS Element, and noninferior 0.10 mm for SYNERGY, and 0.13 mm for SYNERGY half-dose.

A total of 625 patients with acute MI (AMI) were randomized (2:1) to receive EES or SES in the noninferiority XAMI (Xience V Stent vs. Cypher Stent in Primary PCI for Acute MI) trial (24). The MACE rate was 4.0% for EES and 7.7% for SES; the relative risk was 0.52. One-year cardiac mortality and 1-year incidence of definite and/or probable stent thrombosis of 1.2% was similar for EES and SES ($p = 0.21$). In this all-comer, randomized, multicenter AMI trial, second-generation EES was noninferior to SES, and superiority for MACE was suggested.

A study assessed percutaneous coronary intervention (PCI) for unprotected left main coronary artery (ULMCA) stenosis in routine U.S. clinical practice in 5,627 patients undergoing ULMCA PCI at 693 centers within the National Cardiovascular Data Registry Catheterization Percutaneous Coronary Intervention Registry from 2004 to 2008 (25). ULMCA PCI was performed in 4.3% of patients with ULMCA stenosis. Unadjusted in-hospital mortality rates ranged from 2.9% for elective cases to 45.1% for emergent/salvage cases. By 30 months, 57.9% of the elderly ULMCA PCI population experienced death, MI, or revascularization, and 42.7% died. Patients receiving DES (versus BMS) had a lesser 30-month mortality rate, but the composite of major adverse cardiac events (MACE) was similar.

The etiology of late complications of in-stent restenosis and stent thrombosis is not well defined. Studies have reported that one-third of patients with in-stent restenosis of BMS presented with acute coronary syndromes (ACS), and both clinical and histological studies of DES have demonstrated evidence of continuous neointimal growth during long-term follow-up, which is designated as "late catch-up" phenomenon. Emerging evidence is presented of de novo neoatherosclerosis within stents based on histology, angioscopy, and intravascular images that provide a new insight for the mechanism of late stent failure. In-stent neoatherosclerosis is an important substrate for late stent failure for both BMS and DES, especially in the extended phase. In light of the rapid progression in DES, early detection of neoatherosclerosis may be beneficial to improving long-term outcome of patients with DES implants (26).

Le May et al. (27) evaluated 1,389 consecutive STEMI patients in a single emergency medical system, of whom 822 (59.2%) were directly transported to a primary PCI-capable hospital and 567 (40.8%) transported to a non–PCI-capable hospital first. This resulted in shorter door-to-balloon times for the direct transport to a PCI-capable hospital (median 66 vs. 117 min, $p < 0.001$) and lower 6-month mortality (5.0% vs. 11.5%, $p < 0.001$). This study provides unequivocal support for preferentially transporting MI patients to PCI-capable hospitals.

Mehta et al. (28) compared outcomes in patients with STEMI (n = 1,958) and non–ST-segment elevation ACS (n = 5,063) from the large multicenter randomized RIVAL (Radial vs Femoral Access for Coronary Intervention) trial comparing the femoral and radial access site approaches during PCI. Radial access reduced the primary endpoint,

net adverse cardiac events (MACE) (3.1% vs. 5.2%, p = 0.026), and the secondary endpoint (30-day death, MI, stroke) (2.7% vs. 4.6%, p = 0.031) and mortality (1.3% vs. 3.2%, p = 0.006) compared with the femoral approach in STEMI but not non-STEMI patients. Similarly, Romagnoli et al. (29) randomized 1,001 patients with ST-segment elevation acute coronary syndrome in the RIFLE (Radial versus Femoral Randomized Investigation in ST Elevation Acute Coronary Syndrome) trial to the radial versus femoral approach. The primary endpoint (30-day cardiac death, stroke, MI, target lesion revascularization, and bleeding) was lower with the radial approach (13.6% vs. 21.0%, p = 0.003) as was cardiac mortality (5.2% vs. 9.2%, p = 0.020) and bleeding (7.8% vs. 12.2%, p = 0.026). An accompanying editorial by Bertrand and Patel (30) points out that although mortality appears to be reduced by the radial approach for STEMI patients in both of these trials, further understanding of the mechanism by which this might be occurring is required.

Optical coherence tomography. The International Working Group for Intravascular Optical Coherence Tomography (IWG-IVOCT) Standardization and Validation, comprising more than 260 academic and industry members from Asia, Europe, and the United States, presented a review on the current state of the art and its recommendations on key areas within the IVOCT field as a consensus document (31). This document may be broadly used as a standard reference regarding the current state of the IVOCT imaging modality, intended for researchers and clinicians who use IVOCT and analyze IVOCT data.

Concomitant optical coherence tomography (OCT) and intravascular ultrasound (IVUS) area measurements were performed in a subgroup of patients to compare the diagnostic efficiency of both techniques to fractional flow reserve (FFR) (32). An overall moderate diagnostic efficiency of OCT was found (area under the curve [AUC]: 0.74; with sensitivity/specificity of 82%/63% associated with an optimal cutoff value of 1.95 mm^2). Comparison of the results in patients with simultaneous IVUS and OCT imaging revealed no significant differences in the diagnostic efficiency. In the subgroup of small vessels (reference diameter <3 mm), OCT showed a significantly better diagnostic efficiency (AUC: 0.77) than IVUS (AUC: 0.63) to identify functionally significant stenoses (p = 0.04). In conclusion, OCT has a moderate diagnostic efficiency in identifying hemodynamically severe coronary stenoses. Although OCT seems slightly superior to IVUS for this purpose (particularly in vessels <3 mm), its low specificity precludes its use as a substitute of FFR for functional stenosis assessment.

A study assessed the diagnostic value of OCT in 17 patients with suspected spontaneous coronary artery dissection (SCAD). OCT ruled out the diagnosis of SCAD in 6 patients. In 11 patients, OCT confirmed the presence of SCAD as a double-lumen or intramural hematoma image; only 3 patients presented an intimal "flap" on angiography. OCT readily identified the intimal rupture site, the thickness and length of the intimomedial membrane, the area of the true and false lumen, and the associated intramural hematoma and thrombi in the true or false lumen (33).

Instantaneous wave-free ratio. Assessment of stenosis severity with FFR requires that coronary resistance be stable and minimized, conventionally by administration of agents such as adenosine. A new study presented an adenosine-independent, pressure-derived index of coronary stenosis severity determined when resistance is naturally minimized at rest (34). In part 1 (39 stenoses), intracoronary pressure and flow velocity were measured both at baseline and adenosine distal to the stenosis; in part 2 (118 stenoses), intracoronary pressure alone was measured. Wave-intensity analysis identified a wave-free period in which intracoronary resistance at rest is similar in variability and magnitude to those during FFR. The resting distal-to-proximal pressure ratio during this period, the instantaneous wave-free ratio, correlated closely with FFR (r = 0.9, p < 0.001) with excellent diagnostic efficiency (receiver-operating characteristic area under the curve of 93%, at FFR <0.8) and specificity, sensitivity, and negative and positive predictive values of 91%, 85%, 85%, and 91%, respectively. Further studies are needed to validate whether the instantaneous wave-free ratio provides a drug-free index of stenosis severity comparable to FFR.

Hypercholesterolemia and metabolic syndrome. Serum proprotein convertase subtilisin kexin 9 (PCSK9) binds to low-density lipoprotein receptors (LDLR), increasing serum low-density lipoprotein cholesterol (LDL-C). SAR236553 is a fully human monoclonal antibody to PCSK9. A Phase 2 double-blind, parallel-group, placebo-controlled trial randomized 183 patients with LDL-C >100 mg/dl on stable-dose atorvastatin 10, 20, or 40 mg for ≥6 weeks to several dosing regimens of SAR236553 (35). SAR236553 demonstrated a clear dose-response relationship with 40% to 72% LDL-C lowering and substantially reduced non–high-density lipoprotein cholesterol, apolipoprotein B, and lipoprotein(a) [Lp(a)]. SAR236553 was generally well tolerated.

Serum levels of resistin, an adipose tissue-derived adipokine, are increased in human obesity, are positively correlated with atherosclerotic cardiovascular diseases, and down-regulate hepatocyte LDLR expression substantially by >40% in obesity. A key mechanism by which human resistin inhibited LDLR levels, was by increased cellular expression of PCSK9, which enhances intracellular LDLR lysosomal degradation. Resistin diminished statin-mediated up-regulation of the LDLR by 60%, implicating resistin in the relative ineffectiveness of statins in selective target populations (36). These results reveal for the first time that resistin is a highly attractive therapeutic target in ameliorating elevated serum low-density lipoprotein and, thereby, atherosclerotic cardiovascular diseases in obese humans.

A study aimed to examine the effect of resolution from metabolic syndrome (MetS) between youth and adulthood on carotid artery intima-media thickness (IMT) and type 2

diabetes mellitus (T2DM) (37). Of 1,757 patients, those with MetS in youth and adulthood were at 3.4 times the risk of T2DM in adulthood compared with those that did not have MetS at either time-point, whereas those that had resolved their youth MetS status by adulthood showed similar risk to those that did not have MetS at either time-point ($p = 0.20$ for all comparisons). Although youth with MetS are at increased risk of adult high IMT and T2DM, these data indicate that the resolution of youth MetS by adulthood can go some way to normalize this risk to levels seen in those who have never had MetS.

The role of high-density lipoprotein cholesterol in predicting cardiovascular events remains unsettled. Therefore, Mackey et al. (38) evaluated the independent association of high-density lipoprotein (HDL) cholesterol (C) and particle (P) concentrations with carotid IMT and incident coronary artery disease. Both HDL-C and HDL-P correlated with each other and were associated with an increased coronary disease hazard ratio of 0.74 and 0.70, respectively. However, when adjusted for each other and LDL particle concentration, only HDL-P remained independently associated with carotid IMT and coronary heart disease. In an accompanying editorial, deGoma and Rader (39) indicated that the more consistent inverse association between endpoints and HDL-P in this study suggests that direct quantification of the concentration of HDL-P may be useful to refine cardiovascular risk.

Patients with human immunodeficiency virus (HIV) on antiretroviral therapy are at increased risk of atherosclerosis due to metabolic disorders. Therefore, Lazzaretti et al. (40) studied whether dietary intervention could prevent the dyslipidemia associated with antiretroviral therapy in HIV. The diet administered was that recommended by the National Cholesterol Education Program, and the results clearly indicated a beneficial effect as evidenced by a reduction in plasma cholesterol from 190 to 151 mg/dl and LDL from 106 to 85. In an accompanying editorial, Stein (41) comments that nutritional interventions can prevent adverse changes in the lipid profile of HIV-infected patients who are beginning highly antiretroviral therapy, and emphasize the importance of nutritional interventions at this time.

Hypertension and renal denervation. A study investigated the effect of catheter-based renal sympathetic denervation (RD), not only on BP, but also on left ventricular hypertrophy and systolic and diastolic function in patients with resistant hypertension (42). Forty-six patients underwent bilateral RD, and 18 patients served as controls. Besides reduction of systolic and diastolic blood pressure ($-27.8/-8.8$ mm Hg at 6 months, $p < 0.001$), RD significantly reduced left ventricular (LV) mass and improved diastolic function, which might have important prognostic implications in patients with resistant hypertension at high cardiovascular risk.

Carotid and peripheral artery disease. The COBRA (Comparing Two Methods of Expanding Stents Placed in Legs of Diabetics With Peripheral Vascular Disease) trial (43), a prospective, multicenter, randomized, controlled clinical trial of diabetic patients, investigated whether post-dilation of superficial femoral artery nitinol self-expanding stents using a cryoplasty balloon reduces restenosis compared with a conventional balloon. Inclusion criteria included symptoms and superficial femoral artery lesions requiring implantation of stents >5 mm in diameter and >60 mm in length. Primary endpoint was binary restenosis at 12 months. Seventy-four patients were enrolled with 90 stented superficial femoral artery lesions. Mean lesion length was 148 mm, mean stented length was 190 mm, mean stent diameter was 6.1 mm, and 50% of the lesions were total occlusions. At 12 months, binary restenosis was significantly lower in the cryoplasty group (29.3% vs. 55.8%, $p = 0.01$; odds ratio: 0.36.

The YUKON-BTX study (YUKON-Drug-Eluting Stent Below the Knee–Randomised Double-Blind Study) (44) extended the follow-up period of a prospective, randomized, multicenter, double-blind trial comparing polymer-free SES with placebo-coated BMS in the treatment of focal infrapopliteal de novo lesions. The main study endpoint was the event-free survival rate. The mean target lesion length was 31 ± 9 mm. Thirty-five (23.3%) patients died during a mean follow-up period of 1,016 days. The event-free survival rate was 65.8% in the SES group and 44.6% in the BMS group (log-rank $p = 0.02$). Amputation rates were 2.6% and 12.2% ($p = 0.03$), and TVR rates were 9.2% and 20% ($p = 0.06$), respectively. Long-term event-free survival, amputation rates, and changes in Rutherford-Becker class after treatment of focal infrapopliteal lesions are significantly improved with SES in comparison with BMS.

Randomized trials comparing filter-protected carotid artery stenting (CAS) with carotid endarterectomy revealed a higher periprocedural stroke rate after CAS (45). Proximal balloon occlusion may be more effective in preventing cerebral embolization during CAS than filters. Patients ($n = 62$) undergoing CAS with cerebral embolic protection for internal carotid artery stenosis were randomly assigned to proximal balloon occlusion or filter protection. The primary endpoint was the incidence of new cerebral ischemic lesions assessed by diffusion-weighted magnetic resonance imaging. Compared with filter protection, proximal balloon occlusion resulted in a significant reduction in the incidence of new cerebral ischemic lesions (45.2% vs. 87.1%, $p < 0.001$). Lesions in the contralateral hemisphere were found in 29.0% and 6.5% of patients (filter vs. balloon occlusion, respectively, $p = 0.047$). In this randomized trial of patients undergoing CAS, proximal balloon occlusion as compared with filter protection significantly reduced the embolic load to the brain.

Utilizing the National Cardiovascular Data Registry (NCDR) CARE Registry, Hawkins et al. (46) developed and validated a pre-procedural risk quantification score to predict inpatient risk of stroke or death after carotid artery stenting ($n = 11,122$ procedures; 271 events). Independent

predictors of risk included impending major surgery, prior stroke, age, symptomatic lesion, atrial fibrillation, and absence of prior ipsilateral carotid endarterectomy. The model had moderate discriminatory ability (C-statistic 0.71) regardless of symptomatic status or angiographic variables. The NCDR CAS score using 6 clinical variables predicts in-hospital stroke/death following carotid artery stenting.

In an interesting viewpoint, Gress (47) raises the question of the significance of asymptomatic diffusion-weighted imaging abnormalities seen on cerebral magnetic resonance imaging in up to 30% of patients after carotid artery stenting or endarterectomy. Could these be signs of acute ischemic injury that predispose to long-term neurological sequelae? The author calls for more research on the subject, especially in light of the vast number of cardiovascular angiographic procedures performed annually.

Lu et al. (48) report on their series of 41 consecutive patients with ascending aortic arch dissection of whom 15 (10 with chronic dissection and 5 with acute) were judged to be poor surgical candidates. All 15 of these patients were successfully treated by endovascular techniques and placement of stent grafts. At a median follow-up of 26 months (range 16 to 35 months), there was no mortality and only 1 patient required reintervention. This provides an alternative treatment option for the inoperable patient with ascending aortic arch dissection.

Stabile et al. (49) treated 39 consecutive patients with in-stent restenosis (lesion length 82.9 ± 78.9 mm) of the superficial femoral artery with the paclitaxel drug-eluting balloon (IN.PACT, Medtronic, Minneapolis, Minnesota). There were no procedural complications, 100% procedural success, and 12-month primary patency of 92.1% and secondary patency 100%. These findings are promising because contemporary treatment of in-stent restenosis of the superficial femoral artery has been limited due to high recurrent restenosis rates.

Scheinert et al. (50) randomized 200 patients (lesion length 27 ± 21 mm) with critical limb ischemia to infrapopliteal sirolimus-eluting stent versus percutaneous balloon angioplasty. At 1 year, lower angiographic restenosis (22.4% vs. 41.9%, $p = 0.019$), and greater vessel patency (75.0% vs. 57.1%, $p = 0.025$), but similar rates of death, repeat revascularization, and index-limb amputation rates, were observed with sirolimus-eluting stents. This offers a potentially superior option to balloon angioplasty alone for below-the-knee lesions in critical limb ischemia.

Rogers et al. (51) evaluated the safety and feasibility of zotarolimus-eluting stent implantation in focal atherosclerotic lesions of the internal pudendal arteries among 30 men with erectile dysfunction and suboptimal response to phosphodiesterase-5 inhibitors. In this first-in-man ZEN trial, procedural success was 100%, and there were no major adverse events at 6-month follow-up. The primary feasibility endpoint (International Index for Erectile Dysfunction improvement ≥4) at 3 months was achieved in 59.3% in the intention-to-treat cohort and 68.2% in the per protocol cohort. Binary restenosis was observed in 34.4% and 30.8% of lesions in the 2 groups, respectively. In an accompanying editorial, Shishehbor and Philip (52) caution that the use of drug-eluting stents for the treatment of erectile dysfunction remains investigational, but this study sets the stage for an appropriately powered randomized clinical trial.

Antiplatelet therapy. The RESET (REal Safety and Efficacy of a 3-month dual antiplatelet Therapy following E-ZES implantation) trial (53) evaluated shorter duration (3 months) dual antiplatelet therapy (DAPT) after DES implantation in 2,117 randomly assigned patients with coronary artery stenosis into 2 groups according to DAPT duration and stent type: 3-month DAPT following Endeavor zotarolimus-eluting stent (E-ZES) implantation (E-ZES + 3-month DAPT) versus 12-month DAPT following the other DES implantation (standard therapy). The primary endpoint occurred in 40 (4.7%) patients assigned to E-ZES + 3-month DAPT compared with 41 (4.7%) patients assigned to the standard therapy ($p < 0.001$ for noninferiority). The composite rates of any death, MI, or stent thrombosis were 0.8% and 1.3%, respectively, stent thrombosis rates were 0.2% and 0.3%, respectively ($p = 0.65$), without its further occurrence after cessation of clopidogrel in the E-ZES_3-month DAPT group. The rates of TVR were 3.9% and 3.7%, respectively; E-ZES + 3-month DAPT was noninferior to the standard therapy with respect to the occurrence of the primary endpoint.

Another study assessed the risk associated with DAPT discontinuation, and specifically, temporary discontinuation, during the first year after DES implantation (54). A total of 1,622 consecutive patients undergoing DES implantation were followed up at 3, 6, 9, and 12 months to record the 1-year antiplatelet therapy discontinuation (ATD) rate, the number of days without DAPT, and the rate of 1-year major cardiac events. One hundred seventy-two (10.6%) patients interrupted at least 1 antiplatelet drug during the first year after DES implantation. Most (64.5%) interrupted DAPT temporarily (median: 7 days). Discontinuation was followed by ACS in 7 (4.1%; a similar rate of MACE to that in patients without ATD). ATD was not independently associated with 1-year MACE. ATD within the first year and beyond the first month after DES is not exceptional, is usually temporary, and does not appear to have a large impact on risk.

The ISAR-REACT 4 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment-4) platelet substudy aimed to determine the relevance of high on-clopidogrel treatment platelet reactivity (HPR) in non–ST-segment elevation MI patients that received abciximab with unfractionated heparin or bivalirudin during PCI (55). For abciximab with unfractionated heparin, the incidence of the efficacy endpoint (death, MI, urgent TVR) was similar in HPR versus no-HPR patients (9.4% vs. 6.7%). For bivalirudin, the incidence of the efficacy endpoint was significantly higher in HPR versus no-HPR patients (22.0% vs. 5.0%; odds ratio: 5.4; $p < 0.0001$). For

patients with a risk profile similar to the subjects enrolled in this platelet substudy, the impact of HPR on clinical outcomes may depend on the type of adjunctive antithrombotic therapy used during PCI.

In a prospective, single-center, single-blind study, 44 ACS patients with HPR while on clopidogrel 24 h post-PCI were randomized to either ticagrelor 90 mg twice daily or prasugrel 10 mg once daily for 15 days with a crossover directly to the alternate treatment for another 15 days (56). HPR was defined as platelet reactivity units (PRU) >235 as assessed by the VerifyNow P2Y12 function assay (Accumetrics, San Diego, California). The primary endpoint of platelet reactivity at the end of the 2 treatment periods was lower for ticagrelor (32.9 PRU) compared with prasugrel (101.3 PRU). The secondary endpoint of HPR rate was 0% for ticagrelor and 2.4% for prasugrel (1 of 42, p = 0.5). No patient exhibited a major bleeding event in either treatment group. In patients with ACS exhibiting HPR while on clopidogrel 24 h post-PCI, ticagrelor produces a significantly higher platelet inhibition compared with prasugrel.

The GIFT (Genotype Information and Functional Testing Study) study sought to evaluate the influence of single nucleotide polymorphisms (SNPs) on the pharmacodynamic effect of high- or standard-dose clopidogrel after PCI (57). DNA samples obtained from 1,028 patients were genotyped for 41 SNPs in 17 genes related to platelet reactivity. After adjusting for clinical characteristics, *CYP2C19**2* was significantly associated with HPR at 12 to 24 h, 30 days, and 6 months after PCI, whereas *PON1*, *ABCB1 3435 C→T*, and other candidate SNPs were not. Carriers of 1 and 2 reduced-function *CYP2C19* alleles were significantly more likely to display persistently high on-treatment reactivity (OTR) at 30 days and 6 months, irrespective of treatment assignment. The portion of the risk of persistently high OTR at 30 days attributable to reduced-function *CYP2C19* allele carriage was 5.2% in the patients randomly assigned to high-dose clopidogrel. *CYP2C19*, but not *PON1* or *ABCB1,* is a significant determinant of the pharmacodynamic effects of clopidogrel, both early and late after PCI. In patients with high OTR identified by platelet function testing, the *CYP2C19* genotype provides limited incremental information regarding the risk of persistently high reactivity with clopidogrel 150 mg maintenance dosing.

The effects of different proton pump inhibitors on clopidogrel were studied by Frelinger et al. (58). A cross-over design was utilized in normal subjects with the evaluation of platelet activity by VASP, adenosine diphosphate stimulation, and VerifyNow. Clopidogrel active metabolite decreases significantly with esomeprazole, but not with dexlansoprazole or lansoprazole. Thus, these agents might be preferable in patients being treated with clopidogrel.

Prior studies have demonstrated that greater reduction of platelet reactivity with prasugrel reduces events at the cost of increased bleeding in acute coronary syndrome. Smith et al. (59) expanded the database of the TRITON-TIMI 38 study (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38) to characterize bleeding in patients who receive prasugrel. They demonstrated that despite causing an increase in observed bleeding, platelet transfusion, and surgical re-exploration for bleeding, prasugrel was associated with a lower rate of death after coronary artery bypass grafting (CABG) compared with clopidogrel. In a similar study, Trenk et al. (60) examined the efficacy, safety, and antiplatelet effect of prasugrel in patients with high on-treatment platelet reactivity after percutaneous intervention in the TRIGGER-PCI study (Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy with Prasugrel). In patients with high-platelet reactivity following loading doses of clopidogrel, prasugrel provided an enhanced platelet inhibition but did not result in a reduction of adverse ischemic events after PCI with DES. Perhaps the most important finding of this study was the very low rate of adverse events after PCI with current therapy with either agent, being <0.5%. Given the greater antiplatelet potency of prasugrel, Price et al. (61) examined the recovery of platelet function after discontinuation of these agents in the Recovery Trial. These investigators observed that after 7 days of either 10-mg prasugrel or 75-mg clopidogrel, >75% of patients returned to baseline reactivity within 5 days with clopidogrel but required 7 days with prasugrel. These data provide strong support for the recommendation to delay major surgery for this period of time for the individual antiplatelet agents. Tello-Montoliu et al. (62) administered 10-mg, 30-mg, and 60-mg doses of prasugrel to test the pharmacodynamic effects of reloading dose of prasugrel in patients already on maintenance therapy. They found that the 60-mg dose was associated with faster and greater platelet inhibition, therefore establishing a recommendation for reloading of this agent.

Sachdeva et al. (63) studied the impact of clopidogrel discontinuation in patients undergoing saphenous vein graft PCI. In a cohort study of 603 patients who underwent vein graft PCI from 2000 to 2009, 411 patients were event free at the time of clopidogrel cessation. After multivariable analysis, the incident rate ratio (95% confidence interval [CI]) for death and death/myocardial infarction 0 to 90 days after clopidogrel discontinuation compared with 91 to 365 days was 2.33 (1.32 to 4.11) and 2.58 (1.64 to 4.07), respectively. Therefore, a clustering of ischemic events is observed soon after clopidogrel discontinuation in patients undergoing vein graft PCI.

Previous modeling data have suggested that prasugrel 5 mg in low body weight patients would be noninferior to prasugrel 10 mg in high body weight patients. In the FEATHER (Comparison of Prasugrel and Clopidogrel in Low Body Weight Versus Higher Body Weight With Coronary Artery Disease) study, Erlinge et al. (64) performed a blinded 3-period cross-over study in stable coronary artery disease (CAD) patients being treated with

JACC Vol. 61, No. 3, 2013
January 22, 2013:357–85

aspirin by administering prasugrel 5 mg and 10 mg, and clopidogrel 75 mg to low body weight (56.4 ± 3.7 kg, n = 34) and high body weight (84.7 ± 14.9 kg, n = 38) subjects. Median maximal platelet aggregation by light transmission aggregometry (primary endpoint) for prasugrel 5 mg in low body weight patients (47.0%) was noninferior to the 75th percentile for prasugrel 10 mg in high body weight patients (57.1%), and mean maximal platelet aggregation was similar. This pharmacodynamic study supports the use of prasugrel 5 mg in low body weight patients.

Singla et al. (65) provided a "state of the art" review regarding the risks of adverse ischemic and bleeding events after noncardiac surgery in patients with previous PCI. They point out the consensus in the literature regarding the high risk of stent thrombosis in patients undergoing noncardiac surgery with either bare-metal or drug-eluting stents in the first 4 weeks after PCI. Otherwise, there is paucity of evidence-based data on the best management of antiplatelet therapy for noncardiac surgery beyond the first month after PCI. The best current treatment algorithm based on contemporary data is to delay elective noncardiac surgery beyond 1 year after PCI with drug-eluting stents and beyond 1 month after PCI with a bare-metal stent. For patients requiring noncardiac surgery before that time, aspirin and preferably dual antiplatelet therapy should be continued through the surgery.

With the availability of multiple new antithrombotic agents, the question of comparative efficacy and safety when used for stroke prevention and atrial fibrillation (AF) begged to be answered. Therefore, Lip et al. (66) carried out indirect comparisons for the oral direct thrombin inhibitor dabigatran and the oral factor Xa inhibitors rivaroxaban and apixaban compared with warfarin for stroke prevention in AF. Acknowledging the limitations of indirect comparison, they reported no profound significant differences in efficacy between the apixaban and dabigatran or rivaroxaban. Dabigatran 150 mg twice daily (BID) was superior to rivaroxaban for some efficacy endpoints, whereas major bleeding was significantly lower with dabigatran 150 BID or apixaban. In an accompanying editorial (67), Cannon and Kohli point out that indirect comparisons are fraught with a potential danger, and can only serve to be hypothesis generating.

Given the bleeding risk with antithrombotic therapy, Apostolakis et al. (68) compared several risk-prediction scores for bleeding with anticoagulation. Using the data from the AMADEUS (Evaluating the use of SR 34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) trial, they compared the $HEMORR_2HAGES$, the ATRIA and the HAS-BLED risk scores in patients with atrial fibrillation. Although the authors observed that the HAS-BLED score was superior to the other 2, the most compelling conclusion from this study was that none of the risk scores were of great value in predicting clinically relevant bleeding. In regard to risk, brief correspondence from Price et al. (69) reported 2 patients in whom thrombosis of prosthetic heart valves was associated with the conversion from warfarin to treatment dabigatran at usual doses. Until extensive studies evaluating the role of dabigatran in patients with prosthetic valves are completed, there is no approval for using this agent.

Heart failure. Many heart failure (HF) and reduced ejection fraction (HFrEF) patients have or develop worsening renal function (WRF) over time, and there is uncertainty among clinicians whether aldosterone receptor antagonists (ARAs) should be initiated and/or maintained in the face of WRF. A study by Vardeny et al. (70) analyzing results from the RALES trial (Randomized Aldactone Evaluation Study) in 1,658 patients with New York Heart Association functional class III or IV HF and an ejection fraction <35% addressed these issues. They found that individuals with reduced baseline estimated glomerular filtration rate (eGFR) exhibited similar relative risk reductions in all-cause death and the combined endpoint of death or HF hospitalization as those with a baseline eGFR >60 and greater absolute risk reduction compared with those with a higher baseline eGFR. WRF was associated with an increased adjusted risk of death in the placebo but not the spironolactone group. In an accompanying editorial (71), Kiernan and Konstam noted that these data provide reassurance regarding the relative safety and benefit of ARAs in HFrEF patients with moderate chronic kidney disease but urged clinicians to continue to use caution in using ARAs.

Chen et al. (72) performed a randomized double-blind study comparing 8 weeks of chronic subcutaneous administration of B-type natriuretic peptide (BNP) (10 μg/kg BID) (n = 20) with placebo (n = 20) in patients with ejection fraction <35% and class II to III HF. Chronic SC BNP significantly reduced LV systolic and diastolic volume index and LV mass index, and was associated with a significantly greater improvement of Minnesota Living with HF score, E/e′ ratio, and decreased left atrial volume index. An accompanying editorial by Ahmad and Felker (73) noted that although these results seem to contradict previous trials in which BNP failed to provide clinical benefits, a lower dose and more constant exposure to the drug was used in this pilot, and the authors concluded by endorsing the need for future studies.

Although evidence indicates that newer therapies for breast cancer increase the likelihood of HF, most data have been collected in trials in which trastuzumab was administered to younger patients, often in combination with anthracycline chemotherapy. Chen et al. (74) abstracted 16 tumor registries linked to Medicare to calculate the 3-year incidence of HF or cardiomyopathy (CM) in women age 67 to 94 with early breast cancer. Of the 45,537 patients, they found that the incidence rates for HF/CM were higher for trastuzumab (32.1%) or trastuzumab in combination with anthracycline (41.9%) compared with no adjuvant therapy (18.1%). They concluded that HF or CM was more common after trastuzumab therapy for older women with early breast cancer than in clinical trials that included mostly younger women. In an accompanying editorial (75), Lenihan commented that these results indicated that trastu-

zumab, anthracyclines, and their combination have to be considered as major risk factors for the development of HF/CM and that this treatment should identify the patient as Stage A. Previous studies in-vitro and in animal models have suggested that statins might be one way to reduce HF risk in patients receiving chemotherapy. Seicean et al. (76) identified a cohort of patients with newly diagnosed breast cancer treated with anthracyline. After adjusting for other risk factors, they found a significantly lower risk of HF hospitalization in the patients who received statin therapy than in controls. They also found that cardiotoxicity risk factors at the time of diagnosis, baseline ejection fraction, and trastuzumab use were predictors of incident HF. In an accompanying editorial, Lenihan (77) commented upon the growing acceptance that statins may improve cancer outcomes and that they "appear to be one necessary component for cancer patients to ready themselves for their cancer war."

It is not known whether severely ill patients with advanced heart failure and anemia are likely to respond to iron alone or whether the addition of erythropoiesis-stimulating agents (ESA) is also necessary. To address this issue, Terrovitis et al. (78) randomly assigned 30 iron-deficient patients with advanced HFrEF to treatment with either the combination of iron and an ESA or iron alone. There was a significant increase in hemoglobin that persisted to 3 months without serious adverse effects with either regimen. The investigators concluded that monotherapy with intravenous iron should be regarded as an efficient treatment option for iron deficiency anemia in patients with advanced heart failure. Although both cardiopulmonary exercise testing and 6-min walk testing (6MW) have been used to assess functional capacity in heart failure patients with HFrEF, there is limited information comparing the 2 tests. Forman et al. (79) evaluated 2,054 patients who underwent both tests in the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise TrainNing) study. They found that in HFrEF patients, cardiopulmonary exercise testing and 6 MW testing indices were as univariate predictors for all-cause mortality and all-cause hospitalization/mortality. Both indices added only modest prognostic discrimination to models that included important demographic and clinical covariates. Logistical restraints often limit the ability to perform formal tests of exercise capacity and hospitalized patients may not be able to perform such tests optimally. Spruit et al. (80) evaluated the extent of patient reported ability to perform daily activities using the Duke Activity Status Index and 6MW test distance change over 1 year and whether such changes affected prognosis in chronic heart failure patients. In a group of 309 patients, they found that improved self-reported physical capacity after 1 year was associated with better prognosis in HF patients. By contrast, objective measures of improvement appeared to have limited prognostic value. These findings support the use of a questionnaire such as the Duke Activity Status Index to estimate self-reported physical capacity in daily clinical practice.

Several studies deal with issues related to cardiac rate and rhythm and heart failure. The TARGET trial (Targeted Left Ventricular Lead Placement to guide Cardiac Resynchronization Therapy) (81) examined the premise that placement of the left ventricular lead at the site of the latest contraction away from the scar would confer the best response to resynchronization (CRT). They randomized 220 patients, were able to place the LV lead in the site of latest peak contraction in approximately 60%, and found that group to have a greater number of responders at 6 months (70% vs. 50%, $p < 0.03$) and greater number with a 15% reduction in LV end-systolic volume (2% vs. 28%). These data suggest that placing the left ventricular lead for resynchronization in the segment of latest contraction may substantially reduce the number of nonresponders to resynchronization therapy. In an accompanying editorial, Ghali (82) indicates that although the findings of this trial may not mandate placement in the most delayed viable segment when CRT is being considered, they do indicate that some reason for not following this strategy should be existent. A substudy of the SHIFT (Systolic Heart Failure Treatment with the I_f inhibitor ivabradine Trial) study addresses the important question of whether or not the ability of ivabradine to have a beneficial effect in congestive heart failure patients was influenced by the dose of beta-blocker drug (83). Patients in SHIFT were grouped according to beta-blocker doses: <25%, 25% to 50%, 50% to 100%, and 100%. The primary endpoint of heart failure hospitalization was reduced by ivabradine in all subgroups. Thus, the authors concluded that the magnitude of heart rate reduction by beta-blocker plus ivabradine, rather than background beta-blocker dose, primarily determines the subsequent effect on outcomes. In an accompanying editorial (84), Sarraf and Francis comment that despite the observation that reduction in heart rate appears to be the most important outcome, it would be well to avoid "indication creep" in which ivabradine was substituted for beta-blockers in patients who harbor mild but relative contraindications to beta-blockers.

A major advance in the optimal management of patients with continuous–flow left ventricular assist devices (LVAD) was the Columbia Ramp Study by Uriel et al. (85). This paper described a protocol applied in patients with LVADs to optimize the continuous-flow rate and detect device malfunction. The rotational rate of the device was increased in increments of 400 rpm from 8,000 to 12,000 rpm while LV end-diastolic dimension, aortic valve opening, valve insufficiency, blood pressure, and LVAD parameters were recorded. The results were subsequently plotted and linear function slopes developed. The rotational speed was changed on the basis of these tests in 61% of patients, whereas device thrombosis was confirmed in 8 of 10 cases suspicious by the results of the test. In an accompanying editorial, Rogers and Milano (86) comment that as mechanical circulatory support continues to mature, development and validation of objective optimization approaches like the Ramp Study are needed.

JACC Vol. 61, No. 3, 2013
January 22, 2013:357–85

Electrophysiology. Priori et al. (87) reported on 308 patients with Brugada syndrome in the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) study, and identified the most significant predictors of ventricular arrhythmias to identify good candidates for an implantable cardioverter-defibrillator. This was a prospective registry study, and patients underwent programmed electrical stimulation in an attempt to induce potentially life-threatening arrhythmias. The authors found that programmed electrical stimulation of ventricular arrhythmias was not useful in identifying Brugada patients at risk for future arrhythmias. The useful variables were a spontaneous type 1 Brugada pattern on the electrocardiogram (ECG), a history of syncope, a ventricular effective refractory period <200 ms at electrophysiology study, and QRS fragmentation on ECG. This study also identified 2 new independent risk factors, namely, a short ventricular refractory period (which could only be determined at electrophysiological study) and QRS fractionation on ECG. This study suggests that invasive electrophysiological testing may not be warranted at all in patients with Brugada syndrome to predict risk of ventricular arrhythmias and need for ICD implantation.

Brignole et al. (88) reported on a prospective observational study of ICD implantation with or without defibrillation threshold testing in 2,120 consecutive patients in the SAFE-ICD (SAFEty of Two Strategies of ICD Management at Implantation) study. Patients were followed up to 24 months for a primary endpoint of severe complications at ICD implant and sudden cardiac death or resuscitation (88). In this population, which may have been low risk to begin with, there was no difference in primary endpoint at the end of follow-up, and there was no difference in mortality from any cause. The authors acknowledge that the sudden death rate was low and may have been insufficient to show a difference in the clinical effect of defibrillation threshold testing, although the shock rate was sufficiently high. In addition, as noted in the accompanying editorial by Estes (89), this study may not have addressed a higher-risk population with high DFTs, and this study did not follow patients beyond 2 years, and in some patients shocks do not occur until after 2 years follow-up.

Ganesan et al. (90) reviewed all-cause and cardiovascular mortality published data from 2004 to 2010 on patients with atrial fibrillation undergoing CRT, with (n = 339) or without (n = 429) atrioventricular (AV) node ablation. The authors concluded that AV node ablation in patients with AF undergoing CRT reduced all-cause mortality with a risk ratio of 0.42, and cardiovascular mortality with a risk ratio of 0.44, and improved mean New York Heart Association functional class with a risk ratio of −0.52. AV node ablation increases the percentage of biventricular pacing, which was noted to be nearly 100% in the AV node ablation patients, but varied from only 82% to 96.5% in the patients without AV node ablation. An accompanying editorial by Gasparini and Galimberti (91) emphasize the apparent benefit of AV node ablation in patients with AF undergoing CRT and recommend that it be "considered a fundamental of a combined strategy to obtain the best results of CRT in this complex HF population."

Old Nordkamp et al. (92) reported their initial experience using a totally subcutaneous implantable cardioverter defibrillator (SQ-ICD), ushering in a new era in ICD therapy. They implanted SQ-ICDs in a total of 113 patients out of a total of 1,300 patients who underwent ICD implantation without a need for bradycardia pacing. Only 6 patients had a secondary prevention indication. The mean LV ejection fraction (LVEF) was 41%. During 18 ± 7 months follow-up, no patients died from arrhythmic causes. Eight patients had a total of 9 episodes of spontaneous sustained ventricular tachycardia (VT) and 36 episodes of spontaneous ventricular fibrillation, all episodes were appropriately detected, and shock therapy was successful in 98% of these episodes. Inappropriate shocks occurred in 15 (13%) patients, mostly due to T-wave oversensing or double counting, most of which was solved by device programming. Complications occurred in 16 (14%) patients, including SQ lead migration, lead erosion, and device infections requiring explantation, although the complication rate decreased over time with operator experience. This brief report of the new SQ-ICD demonstrates its feasibility, effectiveness, and limitations.

Atrial fibrillation mechanisms. The growing epidemic of atrial fibrillation (AF) continues to exact substantial public health implications (93). Several papers in the *Journal* in 2012 provided mechanistic insights for AF that may translate into novel therapy. Swartz et al. (94) examined the relationship between serum markers for collagen I and III synthesis, left atrial (LA) fibrosis and post-operative AF. In 54 patients undergoing cardiac surgery without prior AF history, 18 patients developed post-operative AF. Those who developed AF had greater LA fibrosis with higher LA mRNA transcripts for collagen I and III, and higher serum markers for collagen synthesis, with a linear correlation between LA fibrosis and these markers. Clearly, these results require further validation, but add to the growing link between AF and fibrosis (95), dynamic conduction slowing at the site where human AF initiates (96), and the formation of AF-sustaining rotors in humans (97), whose ablation may substantially increase the efficacy of conventional ablation. These data also support recent data that even patients with "lone AF" exhibit detectable conduction slowing compared with controls (98).

In complementary studies, Deftereos et al. (99) reported a randomized controlled trial to test whether the anti-inflammatory colchicine may reduce AF recurrence after pulmonary vein (PV) isolation in patients with paroxysmal AF. The authors randomized 161 patients to a 3-month post-ablation course of colchicine or placebo. In the first 3 months post-ablation, freedom from AF was 84% in the colchicine group versus 66.5% in the placebo limb. The authors concluded that (expected) reductions in inflammatory markers (C-reactive protein and interleukin-6) from

colchicine may explain these results. As discussed in its accompanying editorial (100), this study is intriguing but requires additional follow-up because AF often recurs late after ablation (101).

Improved results from catheter ablation of atrial fibrillation. Catheter ablation is increasingly applied (102), but methods to improve its success (particularly after 1 procedure) (103) and reduce its complications (104) are needed. Several reports focused on new approaches for the catheter ablation of AF. The CONFIRM (Conventional ablation with or without Focal Impulse and Rotor Modulation) trial (97) showed for the first time that human AF may be sustained after it is triggered by stable electrical spiral waves (rotors) or focal sources. Targeted ablation at pre-identified patient-specific sources alone (focal impulse and rotor modulation [FIRM]) demonstrated, uniquely, that AF could be acutely terminated and rendered noninducible. In 92 patients, FIRM-guided therapy had 82.4% freedom from AF compared with 44.9% in conventional (FIRM-blinded) patients at up to 2 years of follow-up using rigorous implanted ECG monitoring. The short-term results of the CONFIRM trial have recently been validated by independent external groups (105).

In another novel approach to ablation, Pokushalov et al. (106) reported on "hybrid" therapy adding renal denervation to conventional pulmonary vein isolation (PVI). The authors randomized 27 patients with paroxysmal AF and resistant hypertension to PVI with and without renal artery denervation achieved using routine ablation catheters. Patients in the hybrid limb had 69% freedom from AF (9 of 13) versus 29% (4 of 14) in the PVI-only limb, with corresponding reductions in hypertension. The authors concluded that renal artery denervation reduces systolic and diastolic blood pressure in patients with drug-resistant hypertension and reduces AF recurrences when combined with PVI.

A major limitation of PV isolation for AF is that durable isolation of the PVs is difficult to achieve, and PV reconnection is seen in patients with (107,108) and without (109) recurrent AF. Kowalski et al. (110) uniquely examined PV histopathology in patients undergoing surgical PV isolation after previously failed percutaneous PVI. After confirming that PVs often reconnected, the authors reported that PVs may be electrically isolated despite visible ablation gaps and provided evidence for continued injury (nuclear pyknosis and myocytolysis) that may explain late AF recurrence (100). Another interesting surgical study by Pison et al. (111) described "hybrid" AF ablation, combining thoracoscopic with percutaneous ablation to achieve PVI with varying additional lesions, including box lesions around the veins, a mitral isthmus line, a left atrial roof line, and right atrial bicaval line. In this single-center, single-arm, observational study in 26 patients (58% paroxysmal AF, 38% prior procedures), the authors reported an 83% procedural success. An editorial by Calkins (112) discusses how, despite the many additional "patient-tailored" lesions that complicate its mechanistic interpretation and obvious technical difficulties of this potentially laborious approach, the study represents a pioneering approach that may have value in some patients.

It is well recognized that metabolic syndrome and obesity may partly explain the epidemic in AF. Two reports in the *Journal* show that patients with obesity and the metabolic syndrome exhibit higher levels of inflammatory markers (113) and shorter atrial refractory periods (114) that may facilitate AF and explain the lower success rate of conventional PV isolation in these populations. Further mechanistic studies are required to elucidate the precise mechanisms of ablation failure in these patients.

A study by Shah et al. (115) reports the outcomes in more than 4,000 patients undergoing catheter ablation for atrial fibrillation in the United States. The authors report a 5% incidence of periprocedural complications. Rates of readmission for recurrent atrial arrhythmias were 21.% by 1 year and nearly 30% by 2 years. These data suggest that early failure after ablation for atrial fibrillation is common and that better patient selection and quality assurance may be necessary to improve outcomes.

Novel oral anticoagulants for AF. One of the major developments in treating AF patients is the availability of novel oral anticoagulants. In a brief report from the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study, Flaker et al. (116) reported that dabigatran has similar efficacy for patients with permanent (longstanding persistent) AF, persistent AF, and paroxysmal AF. In the context of anticoagulation during AF ablation, Lakkireddy et al. (117) compared dabigatran, held only on the morning prior to ablation, against uninterrupted warfarin in 290 patients undergoing AF ablation at 8 centers. In 145 patients in each limb, the authors reported 3 thromboembolic complications (2.1%) in the dabigatran group versus none in the warfarin group ($p = 0.25$), but a higher major bleeding rate (6% vs. 1%; $p = 0.019$), total bleeding rate (14% vs. 6%; $p = 0.031$), and composite of bleeding and thromboembolic complications (16% vs. 6%; $p = 0.009$) in dabigatran versus warfarin patients. The authors concluded that dabigatran peri-AF ablation procedures increases the risk of bleeding compared with uninterrupted warfarin. A comprehensive editorial by Knight (118) discussed this strategy in comparison to other studied anticoagulation strategies during AF ablation.

Treatment of malignant ventricular arrhythmias. Sudden cardiac arrest from ventricular tachyarrhythmias is the leading cause of death in the Western world. Lethal ventricular arrhythmias are typically re-entrant, and require slow conduction velocity and regions of short repolarization. Few strategies improve conduction velocity. A report by Greener et al. (119) showed that gene transfer of connexin43 in a porcine model of ventricular infarction could improve conduction velocity and prevent the induction of ventricular arrhythmias. An editorial commentary by Saffitz

and Kleber (120) portrayed the potential therapeutic implications of this discovery.

Patients with intractable ventricular arrhythmias ("electrical storm") are very difficult to treat. Di Biase et al. (121) reported on a novel method to minimize the chance of partial-thickness lesions that may leave viable tissue, by generating transmural ablation lesions ("homogenization") via epicardial mapping and ablation as well as endocardial ablation. In 92 consecutive patients with ischemic cardiomyopathy and electrical storm, the authors performed ablation either confined to the endocardial surface, or via endocardial and epicardial ablation. During follow-up of 25 ± 10 months, post-ablation VT/ventricular fibrillation recurrence was lower in the homogenization group (19%) compared with those receiving traditional endocardial ablation alone (47%). This study is of particular interest because epicardial ablation is typically less frequently performed in patients with ischemic versus nonischemic cardiomyopathy (122).

There has been much interest in the role of the autonomic nervous system to modulate ventricular arrhythmias. An intriguing study by Han, et al. (123) examined changes in left stellate ganglionic nerve activity (SGNA) and left thoracic vagal nerve activity after acute MI. The authors implanted radio transmitters to record the SGNA, vagal nerve activity, and electrocardiograms in 9 ambulatory dogs before, then after myocardial infarction. The authors found that MI increased 24-h SGNA and, on autopsy, increased nerve staining for growth-associated protein 43 and synaptophysin. The authors concluded that MI causes significant remodeling of extracardiac autonomic nerve activity, which may contribute to ventricular arrhythmias. Prior reports suggested that left cardiac sympathetic denervation could be used to treat patients with electrical storm (124). A brief report in the *Journal* by Ajijola et al. (125) extends that literature by showing that bilateral cardiac sympathetic denervation may be effective in managing electrical storm when left cardiac sympathetic denervation has been unsuccessful.

Cardiac imaging. It has been hypothesized that the duration of left ventricular early systolic lengthening on echo could identify patients with significant coronary artery disease (126). In 86 patients (50% CAD) 2-dimensional speckle-tracking echo was performed before invasive angiography. The duration of early systolic lengthening was prolonged in the patients with CAD (76 ± 37 ms vs. 38 ± 23 ms, $p < 0.001$), with a reduced global systolic strain (−17.7 ± 3.0% vs. −19.5 ± 2.6%, $p = 0.003$). Of interest, the duration of early systolic lengthening decreased significantly after revascularization (from 76 ms to 64 ms, $p = 0.041$).

Coronary artery calcium score has been shown to provide important prognostic information. Various studies further evaluated the use of calcium score for prognosis. The relation between long-term lipid levels, the lipid genetic risk score, and the coronary artery calcium scores were evaluated in the Framingham Heart Study (127). It was shown that early and long-term average lipid levels were strongly associated with an elevated calcium score; the lipid genetic risk score was associated with lipid levels, but was not predictive of an elevated calcium score.

Another study evaluated the value of risk factors during adolescence to predict later development of coronary artery calcifications (128). In 589 individuals, the risk factors were assessed over the ages of 12 to 18 years. At the age of 40 to 46 years, the coronary artery calcium score was assessed. It was shown that elevated LDL-C and systolic blood pressure levels during adolescence were independent predictors of coronary artery calcium during adulthood. These findings emphasize the importance of early prevention and risk factor modification in childhood (129).

Different studies reported on the clinical value of CT angiography. In a large multicenter study (47 centers, 6,198 patients), the value of stress testing to identify obstructive CAD (defined as >50% stenosis) on CT angiography and invasive coronary angiography was evaluated (130). The predictors for a significant stenosis on CT angiography were male sex, smoking, older age, hypertension, and typical angina; importantly, stress test results were not predictive. Furthermore, in a subgroup of 621 patients, there was a strong agreement between CT angiography and invasive angiography for detection of significant stenoses. In an accompanying editorial, it was pointed out that stenosis severity and stress testing reflect different aspects of coronary artery disease (anatomic and functional), and therefore, agreement may be limited (131).

The relative prognostic merits of CT angiography and exercise ECG were retrospectively evaluated in 2,977 patients (132). The median follow-up was 3.3 years, and the 5-year cumulative event rate was 3.6%. Both exercise ECG and CT angiography improved risk stratification over clinical risk factors. However, CT angiography was predictive of future risk independent of exercise ECG results; only in patients with moderate-to-severe stenosis on CT angiography did exercise ECG provide additive prognostic value. In an accompanying editorial, it was emphasized that the role of exercise ECG and CT angiography in the diagnostic algorithm of patients presenting with chest pain and intermediate pre-test likelihood of CAD remains uncertain (133).

A report from the large CONFIRM registry evaluated the role of CT angiography as gatekeeper for invasive coronary angiography (134). In 15,207 patients with intermediate pre-test likelihood of CAD, the use of invasive angiography (and revascularization) paralleled the severity of CAD on CT angiography. In patients with mild CAD on CT angiography, the referral rates for angiography and revascularization were low (8.3% and 2.5%, respectively). Conversely, in patients with obstructive 3-vessel CAD, the referral rates for invasive angiography and revascularization were 69.4% and 66.8%, respectively.

There is also increasing interest in myocardial imaging with CT. The prognostic value of contrast delayed enhancement with 64-slice CT after acute myocardial infarction was evaluated in 102 patients (135). In patients with first acute myocardial infarction, CT imaging was performed immediately after successful percutaneous coronary intervention without the use of additional contrast. The size of myocardial contrast delayed enhancement correlated with outcome, independent of the Thrombolysis In Myocardial Infarction (TIMI) risk score, left ventricular ejection fraction, and the total defect score on nuclear perfusion imaging.

Finally, hybrid imaging permits integration of anatomic and functional (or biological) information and is particularly useful in the field of molecular imaging. Hybrid positron emission tomography/computed tomography (PET/CT) was used in an animal model (pigs) to evaluate changes in angiotensin II subtype 1 receptor (AT1R) after myocardial infarction (136). Using the novel AT1R ligand (^{11}C-KR31173), the feasibility of imaging AT1R was shown; after infarction, there was an AT1R up-regulation in the infracted tissue as compared with the remote area confirmed on postmortem analysis. The safety and feasibility of the PET/CT approach to image AT1R was also demonstrated in humans, although the retention level of ^{11}C-KR31173 was lower than in pigs. Clearly, PET/CT permits imaging on the molecular level and will become important in the improved understanding of pathophysiological processes in health and disease; moreover, visualization of these processes will be useful to evaluate and measure therapeutic effects (137).

In 2012, one of the crucial clinical questions in cardiology is the role of ischemia in determining the need for revascularization. An interesting paper performed in Korea studied the impact of ischemia-guided revascularization (IG) based on the demonstration of perfusion defects by myocardial perfusion imaging (138). The authors used a registry of 5,340 patients who underwent PCI (n = 2,587) or CABG (n = 2,753) and used propensity analysis to compare arteries with corresponding perfusion defects against those without. The incidence of major adverse cardiac and cerebrovascular events (MACE) including death, MI, stroke, or repeat revascularization was significantly lower in the IG group (16.2%) than in the non-IG group (20,7%, p = 0.001), suggesting that IG revascularization guided by myocardial perfusion imaging reduces the rate of MACCE in patients with CAD. The differences were primarily driven by differences in repeat revascularization (9.9% vs. 22.8% in the IG and non-IG groups, respectively, p = 0.009) and particularly in patients who had PCI as opposed to CABG. The paper's findings were further discussed by Weintraub (139), who provided a larger context for study interpretation and potential use in clinical practice.

Myocardial perfusion abnormalities determined by imaging, against which the fractional flow reserve method was validated, represents the best way to assess the flow-limiting capability of specific coronary stenoses. This year, a multimodality meta-analysis by Jaarsma et al. (140) addressed the diagnostic performance of single-photon emission computed tomography (SPECT), cardiac magnetic resonance (CMR), and PET against invasive coronary angiography. Pooled sensitivities were 88%, 89%, and 84% for SPECT, CMR, and PET, with pooled specificities of 61%, 76%, and 81%, respectively. Study characteristics and test characteristics did not appear to affect these results, indicating that PET is probably the modality with the strongest diagnostic profile. Another meta-analysis compared SPECT (8 studies including 1,755 patients) with rubidium-82 PET (15 studies including 1,344 patients) performed by McArdle et al. (141) with pooled sensitivities of 85% versus 90% for SPECT and PET, respectively, whereas pooled specificities were 85% and 88%, respectively. The authors conclude that rubidium-82 PET remains superior to SPECT for the detection of CAD.

Finally, the important head-to-head comparisons between ^{13}N-ammonia PET and CMR by Morton et al. (142) adds significantly to the field of quantitative perfusion analysis. The authors studied 41 patients with both imaging methods before invasive angiography. CMR and PET correlated well for measures of myocardial perfusion reserve (r = 0.75), but absolute perfusion correlated less well at rest (r = 0.32) and during stress (r = 0.37). The authors concluded that despite the good correlations on myocardial perfusion reserve and its utility clinically, significant development is still required before absolute perfusion can be measured accurately by magnetic resonance. In an editorial, Bernard Gerber (143) discussed issues related to the measurement of perfusion reserve noninvasively and the specific contribution of this original paper.

Jogiya et al. (144) reported the validation of a novel 3-dimensional whole-heart magnetic resonance imaging (MRI) perfusion imaging method against fractional flow reserve for the detection of obstructive CAD. The authors found that state-of-the-art MRI perfusion methods have 91% sensitivity and 90% specificity when compared with FFR and also a good correlation between ischemic burden by CMR and the Duke Jeopardy Score (r = 0.82, p = 0.0001). They concluded that state-of-the-art perfusion studies can accurately detect obstructive CAD and thus holds promise for the noninvasive guidance of therapy. Another study reported the use of blood oxygen level–dependent (BOLD) MRI at 3-T to evaluate the actual presence of ischemia in patients with CAD. The prospective study included 60 patients receiving BOLD and first-pass CMR perfusion imaging at rest and adenosine stress versus invasive coronary angiography (145). Importantly, the ischemic threshold for the BOLD method at 3-T was first determined in a preceding study involving 25 patients with CAD. The authors reported a sensitivity of 92% and specificity of 72% for the BOLD technique to detect myocardial ischemia but also to identify obstructive CAD. Interestingly, segment-based analysis demonstrated evidence of dissociation between oxygenation and perfusion,

JACC Vol. 61, No. 3, 2013
January 22, 2013:357–85

with a weaker correlation between BOLD and anatomic stenosis ($r = -0.20$) than with myocardial perfusion ($r = -0.40$, $p < 0.005$). The possibility of reaching beyond anatomic obstruction and perfusion deficits to measure oxygenation supply/demand disequilibrium directly is indeed exciting and may be feasible at higher field strengths. The paper's findings are further evaluated in an accompanying editorial comment by Weinsaft and Spincemaille (146).

In an editorial "Myocardial Viability Imaging: Dead or Alive?" Wu (147) puts in perspective an important study by Gerber et al. (148) on the value of myocardial viability assessment by MRI in the wake of failure to predict clinical outcomes by other imaging methods used in the STICH (Surgical Treatment for Ischemic Heart Failure) trial. Gerber et al. studied 144 patients followed for over 3 years and showed that among patients treated medically, survival was significantly worse in patients with dysfunctional, but viable as opposed to nonviable, myocardium (48% vs. 77%, respectively, $p < 0.02$) (148). Conversely, among revascularized patients, survival was similar whether myocardium was viable or not (88% vs. 77%, p = NS). Moreover, in multivariable analysis, the interaction of revascularization and viability added value (chi-square test: 13.1, $p < 0.0004$) to other clinical predictors of prognosis. Finally, the hazard of death remained greater for patients treated medically than for those treated with revascularization that restored myocardial viability (HR: 2.5). The authors concluded that in patients treated medically, the presence of dysfunctional myocardium assessed by CMR is an independent predictor of mortality.

The use of contrast-enhanced MRI has evolved rapidly to address questions of scar sizing and pathophysiology among patients with nonischemic cardiomyopathies. This year, Todiere et al. (149) reported the progression of myocardial fibrosis measured by CMR among patients with hypertrophic cardiomyopathy (HCM). A total of 55 HCM patients underwent 2 CMR examinations separated by an interval of 719 days. In 44 patients, the extent of myocardial fibrosis increased substantially (>1 g), and patients with apical HCM who had worse heart failure symptoms were particularly prone to scar augmentation. The authors concluded that myocardial fibrosis in HCM can progress fast and is harbinger of worse clinical status. The significance of these findings is discussed in detail in an accompanying editorial comment by Bluemke and Yang (150). Klem et al. (151) report that the evaluation of myocardial scars by MRI improves the risk stratification of patients being considered for cardiac defibrillation implantation. The authors showed that during a median follow-up of 2 years, 137 patients who underwent clinical evaluation for possible ICD implantation suffered adverse outcomes at a faster pace if they had myocardial scar size >5%. Among patients with LVEF ≤30%, those with significant scarring had a higher risk than those with minimal or no scarring (HR: 3.9). Interestingly, those with LVEF ≤30%, but with minimal scarring by CMR, had risk similar to those with LVEF >30% (p = 0,71). The authors concluded that myocardial scarring detected by CMR is an independent predictor of adverse outcomes in patients being considered for ICD placement. The study results were further discussed by Mewton and Chevalier (152).

A study by Hachamovitch et al. (153) examined the role of noninvasive imaging in management in patients with coronary disease in a prospective registry. About half of the patients with the most severe abnormalities were not referred for catheterization, and about one-quarter did not receive aspirin or a lipid-lowering agent. More patients undergoing coronary CT angiography were referred for catheterization after a normal or minimally abnormal study than those undergoing nuclear perfusion imaging. This study suggests that noninvasive imaging, particularly CT angiography, is not used optimally in patients with suspected coronary disease.

Biomarkers. Management of patients presenting with out-of-hospital cardiac arrest has been difficult due to a lack of predictors of neurological recovery. To this end, Einav et al. (154) looked at whether serum s100 beta (s100B) and neuron-specific enolase could add value in predicting outcome after out-of-hospital cardiac arrest. They studied 195 patients, and 23% survived to discharge. Patients with good outcomes had lower levels of s100B and enolase levels, measured on days 1 and 3. An editorial by Comess et al. (155) points out that the main 2 things doctors want to know after arrest are when to cease supportive care and what the prospects are for recovery with continued care. Although the study falls short in answering these questions, it lends support to the idea that biomarkers added to clinical indicators may reduce the level of uncertainty when making these important decisions.

Neuropeptide proenkephalin A (PENK-A) is a neurological marker of disruption of the blood-brain barrier and has been studied in diseases of the central nervous system. Doehner et al. (156) measured PENK-A in 189 patients presenting with acute stroke. Levels were significantly higher in patients with ischemic stroke compared with patients with transient ischemic attacks. Additionally, patients in the highest quartile of PENK-A had increased risk of mortality (HR: 2.40) and of major adverse cerebrovascular and cardiovascular events (HR: 2.23). This and other disruption markers of the blood-brain barrier may be promising targets for diagnosis of stroke as well as potential for treatment.

The advantages of measuring levels of microRNAs (miRNAs) include their stability over time, easy quantification, and potential high sensitivity. To this end, Zampetaki et al. (157) studied 19 candidate miRNAs in 820 at-risk patients from a population survey of individuals living in Bruneck, Italy. In subjects with subsequent myocardial infarction, differential coexpression patterns of circulating miRNAs centered on endothelium-enriched miR-126, with platelets being a large contributor to this

signature. In an accompanying editorial by Engelhardt (158), it is suggested that more studies of this kind are still needed in order to better understand the clinical relevance of these tiny RNA molecules.

Despite aggressive treatments of hypertension and dyslipidemia, cardiovascular events remain a challenging problem. Nadir et al. (159) prospectively studied 300 patients enrolled in a primary prevention clinic to identify silent cardiac target organ damage (cTOD) using a combination of imaging and biomarkers. One or more forms of previously undetected cTOD were present in 34% of subjects. BNP >15 pg/ml and high-sensitivity cardiac troponin T (cTnT) >5.93 ng/l was the best combination of biomarkers for cTOD with a sensitivity of 87%, negative predictive value of 90%, and a specificity of 65%. In an editorial, Richards (160) comments that although this type of phenotyping may not be ready for clinical practice, this trial should help us to design future therapeutic trials by better defining treatment targets and better case selection for recruitment to trials.

Whether small elevations of troponins can predict survival in PCI patients is still under debate. To help answer this question, Watabe et al. (161) used multidetector computed tomography to study the relation between culprit plaque characteristics and troponin elevation after PCI. Positive remodeling and spotty calcification were found to be statistically significant independent predictors of troponin elevation. The added attenuation value of <55 Hounsfield units demonstrated a positive predictive value of 95% and a negative predictive value of 90% for troponin rise. An editorial by Malpeso et al. (162) suggests that validation studies still need to be done with advanced multidetector computed tomography and virtual histology IVUS along with histopathologic features.

Galectin 3 (Gal3) is a beta-galactoside–binding lectin expressed by activated macrophages that mediates collagen deposition and subsequent fibrosis. To examine whether Gal-3 could identify primary prevention candidates at increased risk for heart failure, Ho et al. (163) measured Gal-3 in 3,353 subjects in the Framingham Offspring Cohort. They demonstrated that the risk of new HF over 8 years increased by 28% for each standard deviation increase in log-transformed Gal-3 concentration. An editorial by Morrow and O'Donoghue (164) suggests that further investigation of Gal-3 may lead to advances in our understanding of organ fibrosis (especially cardiac) and remodeling, leading to potential new therapies or early use of existing therapies such as mineralocorticoid antagonists.

High-sensitivity troponins have presented a new "phenotype" of a patient with low levels of circulating troponin indicating subclinical cardiac injury. Rubin et al. (165) used the ARIC (Atherosclerosis Risk in Communities) study to examine cTnT as a phenotype of subclinical cardiac disease. Higher glycosylated hemoglobin was associated with elevated hs cTnT among persons without clinically evident coronary disease, suggesting that hyperglycemia contributes to myocardial injury beyond atherosclerotic coronary disease. In an accompanying editorial, de Lemos and Grundy (166) point out that although some limitations were present, this study should prompt further exploration of the role of chronic hyperglycemia in early pathways leading to heart failure development in both animal and human models.

Prevention, quality, cost-effectiveness. The sequencing of the human genome and the identification of various genetic risk markers has renewed interest in the value of a simple family history of early-onset coronary disease as a risk predictor (family history is not included in the Framingham risk calculator). Ranthe et al. (167) linked the Danish Family Relations Database, which documents kinship of Danish citizens, with the hospital records of the Danish healthcare system to assess the risk associated with a family history of early-onset coronary disease. They found the risk of early-onset coronary disease (<60 years of age) was directly and proportionately related to the number of close relatives with early-onset disease, and that the relationship was stronger for first-degree relatives, even after control for other cardiac risk factors. The specific genetic factors mediating this association are as yet uncertain, but this study underscores the value of taking a good family history. Other, novel risk markers for coronary disease are also of interest, and Tseng et al. (168) examined whether evidence of subclinical hypothyroidism was associated with subsequent coronary disease (168). They used the national laboratory database in Taiwan to identify individuals with an elevated level of thyroid-stimulating hormone but a normal circulating level of thyroxine. Compared with controls, those with subclinical hypothyroidism had 1.68 times the risk of subsequent coronary disease. The observed associations do not prove causation, so further study of this question is warranted.

The efficacy of statin therapy in women has been questioned, in part because relatively fewer women have been enrolled in clinical trials of statins. Kostis et al. (169) addressed this issue by performing a sex-specific meta-analysis of statin trials. They found that the relative risk of subsequent cardiovascular events was reduced to a similar extent in women as in men (23% vs. 19% reduction, both $p < 0.0001$), with no evidence of an interaction of treatment with patient sex. Mora et al. (170) examined data in the large JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial to assess which on-treatment lipid parameters best correlated with subsequent risk of cardiovascular disease (CVD). They found that LDL-cholesterol levels while on statin treatment were highly significant predictors of future risk, with no better prediction from non–HDL-cholesterol, apolipoprotein B, or various ratios of lipid parameters, suggesting that simply measuring on-treatment LDL-cholesterol levels is a reasonable approach to follow. One barrier to use of prescription medications is their out-of-pocket cost to patients. Choudhry et al. (171) compared outcomes of patients in a large self-insured company

JACC Vol. 61, No. 3, 2013
January 22, 2013:357–85

that lowered copayments for statins with outcomes of patients in a control company that did not. Lowering copayments was associated with higher rates of statin use, but also was associated with reductions in the rate of visits to physicians and emergency departments, so there was no increase in overall costs to the insurer. Besides cost, the possibility of adverse effects is another barrier to widespread use of statins, especially with recent data from clinical trials showing a higher incidence of diabetes among patients taking statins. To examine the potential risks and benefits of statins in the general population, Wang et al. (172) used data in the Taiwan National Health Insurance Database to compare outcomes in patients who and did not initiate statin therapy. Over 7 years of follow-up, statin users were more likely to develop diabetes than nonusers (2.4% vs. 2.1%), with a hazard ratio of 1.15, which was similar to the risk found in meta-analyses of randomized trials. Despite the higher risk of diabetes, acute myocardial infarction and major adverse cardiovascular events were reduced, suggesting a favorable balance of risk and benefit.

Exercise has many beneficial effects in patients at risk of coronary disease, and in those who have already developed clinically evident disease. In the randomized UPBEAT (Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy) trial (173), an exercise intervention in patients with coronary heart disease significantly reduced their level of depressive symptoms, on par with the reduction achieved by taking the antidepressant drug sertraline. Further evidence for the beneficial effects of exercise comes from a longitudinal study of over 3,000 healthy adults by Lee et al. (174). They found that patients who maintained or improved their level of physical fitness, determined by serial maximal treadmill tests, had a much lower risk of developing hypertension, metabolic syndrome, and hypercholesterolemia. Conversely, patients who increased their percentage of body fat during follow-up were significantly more likely to develop hypertension, metabolic syndrome, and hypercholesterolemia. High levels of body fat had an adverse effect on mortality in a series of 570 patients referred for cardiac rehabilitation, but the poorest outcomes of all were seen among patients who had low body fat in combination with low lean body mass—frail patients with low muscle mass (175).

Many patients have poorly controlled blood pressure even with several medications. Renal denervation using catheter-based approaches has recently been developed as an intervention for drug-resistant hypertension, but economic implications of this approach have not been well understood. Geisler et al. (176) used a simulation model to project the likely outcomes of using renal denervation in patients with clinical characteristics of the participants of the Symplicity HTN-2 trial (Renal Denervation in Patients With Uncontrolled Hypertension) (mean systolic pressure of 178 mm Hg), and estimated a lifetime cost-effectiveness ratio of $3,100 per quality-adjusted life-year. The incremental cost-effectiveness ratio remained favorable when multiple parameters in the model were varied.

The NCDR of the American College of Cardiology is an enormous voluntary database of value in delineating the trends and quality of cardiovascular practice. However, questions have existed regarding the quality of the data itself. Therefore, Messenger et al. (177) described the process by which the accuracy of the NCDR database is validated. Data are filtered through registry-specific algorithms requiring pre-determined levels of completeness and consistency for data fields, and internal quality assurance protocols enforce data standards. Within each registry, 300 to 625 records are audited annually in 25 randomly identified sites. These data provide considerable evidence validating the completeness and accuracy of the NCDR database.

A paper described trends in the prevalence, awareness, management, and control of hypertension in the United States from 1999 to 2010 (178). Data were largely derived from NHANES (National Health and Nutrition Examination Survey). From 2009 to 2010, the prevalence of hypertension was 30.5% among men and 28.5% among women, whereas the hypertension awareness rate was 69% among men and 80% among women. Hypertension control rate was only 40% for men and 56% for women. Thus, from 1999 to 2010, the prevalence of hypertension remained stable. Although hypertension awareness, management, and control were improved, the level remained poor, and no improvement has been reported since 2007.

The recommendations for antibiotic prophylaxis for infective endocarditis have recently been changed in the United States to markedly restrict the number of patients who should receive this therapy. However, the potential consequences of this change are uncertain. To provide data regarding this issue, Duval et al. (179) studied the temporal trends in infectious endocarditis in 3 regions in France from 1991 to 2008, during which time, a similar restriction in antibiotic prophylaxis was implemented. The incidence of endocarditis remained stable over this time, as generally did the causative organisms. Thus, scaling down antibiotic prophylaxis was not associated with an increased incidence of oral streptococci infectious endocarditis, and these data are encouraging as to what should be expected in the United States. An accompanying editorial by Wang (180) points out that the survey did identify an increased rate of staphylococcus infections in patients without predisposing native valve conditions, likely attributable, not only to increased recreational drug use, but also to increasing rates of hemodialysis and immunosuppression.

The role of pre-participation screening of elite athletes with electrocardiography remains controversial. Taking the major Italian study that provided data demonstrating the efficacy of ECG screening in reducing sudden death, Halkin et al. (181) did a cost-effectiveness analysis of such a strategy were it to be applied in the United States. They came to the provocative conclusion that a similar strategy would cost approximately 10.6 million dollars per life saved. However,

in an accompanying editorial, Pelliccia (182) argued that the enormous cost per life saved was due in large measure to the cost of providing the service in the United States, and that substantial cost reductions to achieve the same purpose could be implemented as were already present in Italy. It is likely that this debate will go on.

Genetics and genomics. A pharmacogenomics study this year from Cresci et al. (183) showed that African Americans treated with a beta-blocker were at increased risk of mortality when harboring a mutation in the beta-2 adrenergic receptor (16R allele) compared with those without the mutation. Cresci et al. followed patients at 22 hospitals on beta-adrenergic blockade after acute coronary syndrome for 2 years. Replicating this finding and designing studies to mechanistically test the hypothesis will be needed. These studies add to a growing list of evidence that mutations in the beta-adrenergic receptors are associated with altered response to beta-blocker therapy (184).

A locus on chromosome 4q25 has been widely associated with atrial fibrillation (185,186). Two noncoding SNPs in the 4q25 locus, rs10033464 and rs2200733, have been replicated in populations of European and Asian descent, and were found to be important in studies this year to stratify individuals responding to antiarrhythmic drug therapy (187). A total of 670 individuals in the Vanderbilt Atrial Fibrillation Registry with a common SNP on chromosome 4q25 (rs10022464) responded less favorably to antiarrhythmic drug therapy (class III antiarrhythmic drugs) than patients carrying the wild-type allele at rs10022464. This finding illustrates how genetic testing stratifies patients. Daubert and Pitt (188) in an accompanying editorial agree with the authors, suggesting a randomized, double-blinded trial is needed to fully test the role of genetic testing for this SNP to determine whether patients will respond to antiarrhythmic drug therapy.

A study from Ritchie et al. (189) provides new evidence in their familial atrial fibrillation study that the rs2200733 SNP on chromosome 4q25 acted as a "modifier" gene. In other words, the presence of a SNP on chromosome 4q25 was helpful in determining whether a patient carrying a rare mutation would eventually develop atrial fibrillation. A succinct and well-written refresher by Judge (190) on the current field of genetics and atrial fibrillation accompanies the paper.

QT prolongation is a serious adverse event of antiarrhythmic drugs. A study from Jamshidi et al. (191) provided new evidence that a SNP (rs10800397) in the gene nitric oxide synthase 1 adaptor protein (*NOS1AP*) is associated with drug-induced QT prolongation. SNPs in *NOS1AP* have previously been associated with QT prolongation interval (192–194). The antiarrhythmic drug driving the majority of the changes in this study is amiodarone. These experiments raise the question of genetic testing to identify patients at increased risk of QT prolongation when they are prescribed an antiarrhythmic drug. A limitation of this study was the small number of patients treated with amiodarone that had ventricular arrhythmia and QT prolongation.

Approaches designed to test the functional impact of more than 1 DNA mutation simultaneously acting on a single cell remain a challenge. Mann et al. (195) address this by modeling the electrical properties of cells with 1 or more mutations in potassium channels. Atrial fibrillation probands (n = 20) and 240 controls were sequenced. Novel variants (both nonsynonymous variants and rare variants) were more prevalent in the cases versus controls. Modeling studies were then completed to determine in silico the electrical properties of these cells with 1 or more mutations. This study identifies novel rare variants associated with atrial fibrillation and also highlights a modeling system to evaluate the impact of multiple variants in a single individual on action potential duration.

Of the 4 lipid categories in humans, LDL-C, HDL-C, and triglycerides are affected by diet. However, plasma levels of Lp(a) are thought to be mediated mainly by genetics (196). High Lp(a) is associated with increased CVD risk. However, the mechanisms through which high plasma levels of Lp(a) increase risk of CVD (thrombosis or atherosclerotic mediated) has been controversial. Helgadottir et al (197). tested the hypothesis that 2 variants in LPA conferred susceptibility mainly to atherosclerosis or to thrombosis, and showed that LPA sequence variants were associated with atherosclerosis and not thrombosis. An accompanying editorial reflects on additional genetic studies with LPA and the current gaps in our understanding re LP(a) biology (198).

Crotti et al. (199) provided an insightful look at genetic testing on the 12 Brugada syndrome susceptibility genes in the largest published cohort of unrelated patients referred for Brugada syndrome genetic testing. The authors found mutations in the gene *SCN5A*, encoding a sodium channel, to be the most prevalent in the patients referred for Brugada syndrome genetic testing (listed in Table 2). Additional rare variants were also identified in *SCN5A*, as well as *CACNA1C* and *KCNE3*. Genetic mutations were harbored in 50% of males under age 20 years in this cohort, much higher than the entire cohort. In sum, these data provide new evidence that a positive *SCN5A* genetic test plus a Brugada ECG pattern (spontaneous or drug-induced type 1) may be sufficient for a clinical diagnosis of Brugada syndrome. The editorial from Kaufman (200) provides an important clinical refresher on Brugada syndrome as well as a critical summary of the article and the cohort examined.

Elevated atrial natriuretic peptide (ANP) has long been a biomarker for increased risk of cardiovascular disease, and increased mortality in patients with heart failure, stroke and ischemic heart disease (201). Barbato et al. (201) provide new evidence for an association between a SNP in ANP (rs5065) and increased susceptibility to acute coronary syndrome and unfavorable prognostic value in coronary artery disease. A curious aspect of this study is that the SNP did not correlate with plasma N-terminal pro-atrial natri-

JACC Vol. 61, No. 3, 2013
January 22, 2013:357–85

uretic peptide levels. This variant is prevalent in 14% to 22% of the population.

Our understanding of the genetic mechanisms leading to dilated cardiomyopathy continues to evolve. Mann et al. (202) characterized a variant R222Q in the *SCN5A* gene in a large kindred with dilated cardiomyopathy, multiple arrhythmias, and premature ventricular complexes. Carriers of the R222Q mutation responded more favorably to amiodarone or flecainide, drugs with sodium-channel blocking properties, compared with standard heart failure therapies.

A state-of-the-art tour de force review for hypertrophic cardiomyopathy provided an up-to-date clinical and molecular summary as well as a practical guide for the clinician for determining when and how to order genetic testing for the hypertrophic cardiomyopathy patient (203). This review contains clear definitions in tables and practical guides to genetic testing to aid in the clinical diagnosis of hypertrophic cardiomyopathy.

The paper, "Risk Factors for Malignant Ventricular Arrhythmias in Lamin A/C Mutation Carriers" from van Rijsingen et al. (204) identifies 4 independent risk factors to facilitate the selection of *LMNA* mutation carriers most likely to benefit from an ICD. These factors include nonsustained VT, LVEF <45% on the first clinical contact, male, and non-missense mutations. The high rate of sudden cardiac death and progression to heart failure is confirmed in this study, furthering the need to better understand the mechanisms behind laminopathies and identify more effective treatment options. Maron and Semsarian (205) accompany this with an aerial view perspective on preventing sudden cardiac death in patients with cardiomyopathies.

The adenosine triphosphate-sensitive K+ (KATP) channel is important metabolically in the heart for matching high-energy phosphates/energy substrate metabolism with cellular electrical activity. The KATP channel is composed of different subunits (Kir6.x) that together form a central channel pore. A major finding of a genomic study by Raeis-Dauve et al. (206) is that expression of Kir6.2, the potassium inward rectifier in the left ventricle, is regulated by tissue hypoxia. An accompanying editorial by Lopaschuk and Jaswal (207) proposes a model in which these data may be part of a larger stress adaptation model whereby hypoxia stimulates HIF-1alpha, leading to increased Kir6.2 expression, remodeling of the proteome/energy metabolism, and a final adaptation to hemodynamic cardiac stress.

Identifying molecular targets to effectively treat thoracic aortic aneurysms is an area of intense research. Das et al. (208) provide new evidence in humans that expression of a pro-inflammatory protein that activates the receptor for advanced glycation end products, S100A12, in a thoracic aneurysm is associated with increased hospital length of stay. When S100A12 was reduced in human aortic smooth muscles in vitro, proinflammatory and proapoptotic regulatory factors were attenuated. These translational studies suggest that S100A12 may be an important target in the field of thoracic aneurysms.

Controversies surrounding 17beta-estradiol (E2) and cardiovascular risk continue to generate discussion. An editorial from Banka (209) frames the current estrogen debate and provides a clear perspective on the sex-specific findings reported by Kararigas et al. (210) showing that estrogen actions in the heart are different between men and women. E2 treatment of male cardiac myocytes led to decreased cardiac function mediated through the stimulation of myosin regulatory light chain interacting protein leading to a decrease in myosin regulatory light chain. E2 levels increase in aging and obese men. How large of an impact E2 levels have on increased risk of cardiovascular disease in aging and obese men is not currently known.

A study by Benn et al. (211) takes a new twist on diabetes as a risk factor for cardiovascular disease. This study showed that SNPs that were associated with nonfasting plasma glucose were associated with increased risk of ischemic heart disease and myocardial infarction (211). This study provides increasing evidence that elevated nonfasting glucose increases the risk of individuals developing ischemic heart disease and a myocardial infarction.

Screening novel DNA variants to functionally define their role in arrhythmias, sudden cardiac death, abnormal calcium handling, and other additional cardiovascular phenotypes has often been challenging. The field has begun to explore the use of human-induced pluripotent stem cells (iPSCs) for this purpose. Lior Gepstein's laboratory (Itzhaki et al. [212]) used human iPSCs from dermal fibroblasts from a catecholaminergic polymorphic ventricular tachycardia (CPVT) patient to model CPVT due to a mutation in a cardiac ryanodine receptor. The human iPSCs were characterized by positive staining for all 3 germ layers, nestin (ectoderm), alpha-fetoprotein (endoderm), and desmin (mesoderm), as well as expression of endogenous pluripotency genes, *OCT4*, *SOX2*, *NANOG*, *FOXD3*, and *REX1*. Action potential recordings and calcium handling differed between control human iPSCs versus human iPSCs from a patient with CPVT. An editorial from Gnecchi and Schwartz (213) place this in context with other recently published work.

A provocative finding from Xu et al. (214) showed that a proapoptotic miRNA, miR-34a, is up-regulated in the bone marrow of individuals following a myocardial infarction. Reduction of miR-34a ex vivo in human bone marrow cells improved the therapeutic benefit of these cells in a murine model of myocardial infarct. These studies begin to explain the important impact of an infarct on the profile of bone marrow cells and how it may alter the efficacy of these cells in healing.

A paper on platelet biology and response to antiplatelet therapy in women provides an excellent overview of the understudied area, including the impact of the menstrual cycle and hormones on platelet biology. The results of most large primary or secondary prevention trials with aspirin

show no differences between sexes. Wang et al. (215) outline sex differences in bleeding associated with antiplatelet therapies, with the majority of studies showing women to be at increased risk. However, as pointed out, these trials/studies are not designed to specifically address sex-specific differences, thus additional confounding factors are likely involved.

A state-of-the-art paper from Voora and Ginsburg (216) reviews the "Clinical Application of Cardiovascular Pharmacogenetics." Cardiologists who prescribe statins, clopidogrel, aspirin, warfarin, beta-blockers, or antiarrhythmic drugs will find this paper easy to follow, timely, and succinct in providing an update on genetic testing for patients, as well as providing an outline of the influence of genetic variation on patients' response to therapy (216).

Stem cell trials for the treatment of cardiovascular disease continue to move forward. Li et al. (217) compared different stem cell types for paracrine potency and efficacy of myocardial repair. Cardiospheres outperformed bone marrow–derived mesenchymal stem cells, adipose-derived stem cells, and bone marrow mononuclear cells. Given that recent stem cell trials showed mixed results with bone marrow–derived mesenchymal stem cells, cardiospheres may be next in line for clinical trials.

Isolating c-kit$^+$ cardiac progenitor cells from the myocardium of heart failure patients, genetically engineering these cells to express a cardiac repair gene, and showing improved efficacy in a mouse model of myocardial infarction represent a new line of experimental approaches combining human progenitor cells, cardiac repair, and genetic engineering (218). Pim-1 kinase, a protein that enhances cell survival and metabolic activity while attenuating apoptosis, augmented the repair potential of human progenitor cells when injected directly into the mouse heart concurrent with a myocardial infarction. The editorial from Bishopric (219) of stem cell trials informs of limitations and gaps in the field, and the importance of this contribution from the laboratory of Mark Sussman.

A state-of-the-art publication from Roberts and Stewart (220) describes genes and coronary artery disease. A table is provided that outlines risk loci for coronary artery disease/myocardial infarction, all discovered by genome-wide association studies (GWAS). A list of common features of coronary artery disease genetic risk variants is also helpful and clear. The clinical utility of the genome-wide association study coronary artery disease risk loci is discussed.

Congenital heart disease. A paper by Feinstein et al. (221) presents a state-of-the-art description of current considerations in the fetus with hypoplastic left heart. Included are the prenatal diagnosis and its impact on outcomes; the importance of understanding the flow patterns in and the implications of obstructed foramen ovale and tricuspid regurgitation as adverse fetal findings; and the impact of fetal diagnosis on prenatal recognition, allowing families to prepare for the child, receive counseling, and genetic testing. The pre-operative stabilization of hypoplastic left heart babies with prostaglandin E1 and strategies to seek overall improved cardiac output includes intubation, hypoventilation with inhaled nitric oxide, and carbon dioxide to increase pulmonary resistance and direct cardiac output to the body. The important evolution of the Norwood strategy, modified Blalock-Taussig; and then the actual Norwood modification with a right ventricle (RV) to pulmonary artery (PA) conduit, now widely used. The Pediatric Heart Network randomized patients to Blalock shunt and to RVPA conduit, in which the RVPA conduit was found to be significantly superior. This review highlights the hybrid interventional catheterization combination approaches using percutaneous ductus arteriosus stenting and bilateral pulmonary artery bands to stabilize these patients. The paper highlights the impact of heart transplantation on this disease and the need for diagnostic studies before the final Northrop completion stage. Lastly, consideration shows Fontan models and the fluid dynamic circulation of wall shear stress, and application of the latest computational simulation tools to better understand this disease and its outcomes.

A review by Pahl et al. (222) used the Pediatric Cardiomyopathy Registry, which has enrolled 3,500 infants, children, and adolescents, all under the age of 18 years with cardiomyopathy from 100 centers, from 1990 to 1995, looking at the potential risk for transplantation and sudden death. The 5-year incidence of sudden death was 3%; the major risk factors were age at diagnosis <14.3 years, LV dilation (which most patients probably had), and LV posterior wall thinning. Patients meeting these criteria should be considered for implantable cardioverter-defibrillator device placement. Fifty-six of the 280 deaths did not have an identifiable cause—some of these were probably sudden deaths rather than deaths due to heart failure. This rate of sudden cardiac death is much lower than that for adults.

A study by D'Udekem et al. (223) reviews a database of patients with univentricular heart from 1990 to 2008 at Royal Melbourne Children's Hospital. Among the risk factors for poor outcome were atrioventricular valve regurgitation, not having transposition, heterotaxy, and right ventricular dominance—which, although the outcomes of this latter group improved over the course of the study, still had the largest risk. In an editorial comment, Backer (224) reviews other reports all pointing out that right ventricular dominance remains a major risk factor, but appears to decrease in risk (as does overall risk) after bilateral cavopulmonary anastomosis.

An interesting paper from Chubb et al. (225) reviews long-term outcomes following catheter pulmonary valvotomy for pulmonary atresia with intact ventricular septum. They had 39 patients, 37 of whom had successful valve perforation—17 had stenting of the ducts. Eight died within the first 35 days, with no deaths thereafter. No late arrhythmias or ischemic events— 87% survived; 25 patients (83% of survivors) now have a biventricular circulation. A

JACC Vol. 61, No. 3, 2013
January 22, 2013:357–85

significant factor in early reintervention was stenting of the duct. There was no catch-up growth in the RV in patients—even those who had a biventricular outcome. Multiple interventions are often required to achieve biventricular circulation, and venting of the duct may reduce hospital stay and repeat procedures.

Another paper presents a series of Ebstein's patients undergoing surgeries occurring between October 1980 and January 2010 (226). Many of them had symptoms including heart failure, tachyarrhythmia not amenable to therapy, atrial septal defect progressive cardiomegaly, and other associated problems. Pre-operative electrophysiology study was performed, and ablation of accessory conduction pathways was performed if indicated; elimination of shunts, including atrial septal defect; selective plication of the atrialized RV; and reconstruction or replacement of aortic valve. Of 81 patients, 65 had tricuspid valve replacements, including mechanical Starr-Edwards, mechanical bileaflet prostheses, and porcine valve more recently. The patients had significant other risk factors—hyperlipidemia, diabetes mellitus, and coronary artery disease (in 15 patients). Seventy-eight patients survived, and 13 died during follow-up, especially those with older age at surgery and lower ejection fraction or history of pre-operative heart failure. Although this surgery may be complex, operations performed in an experienced center can offer a low mortality (around 4%), and produce better results if performed earlier in the evolution of symptomatology of these patients.

A paper by Emani et al. (227) describes patients who were split between traditional single-ventricle palliation and progressive LV recruitment (34 of each). The staged left ventricular recruitment strategy includes initial palliation by a Glenn or hemi-Fontan with resection of endocardial fibroelastosis, treating the mitral valve with valvuloplasty, separating fused papillary muscles, chordal elongation and commissurotomy, as well as performing aortic valvuloplasty, atrial septal resection, and sometimes transcatheter balloon dilation of aortic and mitral valves. Once patients had LV growth, the biventricular procedure included takedown of the aortopulmonary anastomosis, and re-establishment of adequate right and left ventricular outflow tract continuity, sometimes by translocation of the pulmonary artery root into the LV outflow tract and RV outflow tract conduit reconstruction. During the 15 years of study, an increasing number of patients have undergone prenatal LV recruitment by aortic valvuloplasty, and postnatal aortic balloon valvuloplasty. Most of the patients from the time of initial hospitalization for surgery, catheterization, and medical treatment had 94 in-house days, but of the 34 gradual LV recruitment patients, 15 ended up having Fontan and left heart rehabilitation, 12 of whom proceeded to a biventricular conversion. This is a single-center study, employing an aggressive strategy, by a well-qualified team, resulting in significant patient rehabilitation to a biventricular outcome in a group that traditionally rarely goes beyond the Fontan stage.

A paper in press by Bautista-Hernandez et al. (228) presents a pilot experience with atrioventricular valve annular remodeling with a bioabsorbable ring for regurgitation in 6 small children. Four children had previously had AV canal repair (2 heterotaxy, 1 Shone's complex), 1 had a dysplastic mitral valve, and 1 had hypoplastic left heart syndrome. Four patients required reoperation—2 unrelated to the AV valve (aortic valve replacement and Fontan completion). In 2 redo patients, the bioring was observed to be fully reabsorbed and replaced with firm fibrotic tissue in the intra-annular position, confirming the valve was growing at a respectable rate. The conclusion of this paper was also supported by quoting a larger experience in Europe.

General topics. Ivabradine is a chronotropic agent that blocks the I_f current and slows heart rate by mechanisms distinct from other drugs, such as beta-adrenergic receptor or calcium channel blockers. Inappropriate sinus tachycardia (IST) is a p syndrome that causes an inappropriate increase in sinus rhythm at rest or with exercise out of proportion to physiological demands, resulting in palpitations that are difficult to treat. In a randomized, double-blind crossover trial, Cappato et al. (229) treated 21 subjects (average age 37 years old) with symptomatic IST with ivabradine 5 mg twice daily or placebo for 6 weeks. Ivabradine significantly reduced heart rates at rest, with standing, during exercise, and 24-h mean heart rate, and reduced symptoms by more than 70%, including palpitations, pre-syncope, dyspnea, and fatigue. Exercise performance improved, and there were minimal side effects from treatment. Scheinman and Vedantham (230) note these results provide "a ray of hope" treating IST, a rare syndrome with disabling symptoms that can be frustratingly difficult to control.

Blood pressure (BP) is modified with aging as arterial stiffness increases. Benetos et al. (231) addressed the prognostic value of different measures of BP and arterial stiffness on cardiovascular risk and morbidity in the longitudinal multicenter PARTAGE (Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population) study. Central BP and aortic pressure waveforms, pulse pressure and pulse pressure amplification were measured by carotid and femoral artery tonometry in 1,126 elderly subjects (874 women) over 80 years old. Two-year mortality (primary endpoint) and major cardiovascular (CV) events were higher in patients with decreased pulse pressure amplification, whereas neither systolic BP, diastolic BP, nor pulse pressure were predictive. A 10% increase in pulse pressure amplification was associated with a 24% decrease in total mortality and a 17% decrease in major CV events. These data suggest that an overly aggressive focus on controlling routine BP measures may lead to iatrogenic complications without a beneficial reduction of CV events or mortality.

Exposure to air pollution may have acute and long-term cardiovascular effects. Krishnan et al. (232) examined the vascular effects of short- and long-term exposure to fine particulate matter <2.5 μm in size ($PM_{2.5}$) in a subset of

3,392 of 6,489 participants from MESA (the Multi-Ethnic Study of Atherosclerosis). An increase in long-term exposure to fine particulate matter ($PM_{2.5}$) was associated with a decrease in brachial artery flow-mediated dilation (FMD), a measure of vascular endothelial function. Changes in FMD were independent of other traditional risk factors. These results indicate that long-term exposure to air pollution alone impairs endothelial function. Brook and Rajagopalan (233) place the importance of these results in the context of current levels of air pollution. The study reported a 3 $\mu g/m^3$ average annual increase in $PM_{2.5}$ exposure caused a 0.3% reduction in FMD. Although the reduction in FMD may seem small, the magnitude of this effect is similar to the adverse risk of smoking or 5 years of aging.

Perioperative statins reduce post-operative complications of cardiac surgery, including atrial fibrillation. Antoniades et al. (234) examined the potential mechanism for statins to suppress oxidative stress. In 303 patients undergoing cardiac surgery, myocardial redox state was assessed by measuring nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, myocardial superoxide anion (O_2^-), and peroxynitrite ($ONOO^-$) from the right atrial appendage. An increase in myocardial redox state was independently associated with increased incidence of post-operative atrial fibrillation, inotropic support, and hospital stay. In a randomized control trial with 42 statin-naive patients, treatment with atorvastatin 40 mg/day compared with placebo for 3 days before coronary artery bypass surgery decreased NADPH oxidase activity and myocardial O_2^- and $ONOO^-$. Ex vivo studies in right atrial appendage tissue demonstrated that atorvastatin inhibited NADPH oxidase by a Rac1-mediated mechanism. It was concluded that pre-operative statins reduce post-operative complications from cardiac surgery by reducing NADPH oxidases to decrease superoxide anion (O_2^-) and peroxynitrite ($ONOO^-$) production. Laufs and Adam (235) note the rapid beneficial effects of statins, which are unrelated to cholesterol lowering, represent new indications based on the "pleiotropic" effects of statins.

Angiotensin-converting enzyme inhibitors (ACEI) reduce cardiovascular events in patients at high risk, a mechanism that may involve platelets. Willoughby et al. (236) examined this in a randomized control trial in 119 of patients with coronary or vascular disease and/or diabetes and 1 additional risk factor treated with ramipril (10 mg) or placebo for 12 weeks. There was no difference in platelet aggregation, but ramipril increased platelet responsiveness to nitric oxide (NO) in the subgroup with platelet NO resistance at baseline and also reduced arterial stiffness and asymmetric dimethylargine (ADMA) levels, a marker of endothelial dysfunction. In second part of the study, these results were confirmed by finding that ramipril improved platelet NO responsiveness. These finding may provide mechanistic insights as to the beneficial effects of ACEI in high-risk patients. Angiolillo and Capodanno (237) comment that this adds to ACEI effects on vasomotor function.

The time course and spatial distribution of inflammatory responses to myocardial infarction can be tracked in vivo by advanced imaging techniques. Lee et al. (238) used hybrid PET and MRI to demonstrate a 5- to 6-fold increase in macrophage/monocyte infiltration in noninfarcted remote myocardium that peaked on day 10 in mice following myocardial infarction. This was associated with an increase in recruiting adhesion molecules and chemokines and matrix metalloproteinase activity. Similar findings were observed in human hearts, with increased macrophage infiltration in the remote region following myocardial infarction. The recruitment of monocytes to remote zone may play an important role in post-MI dilation and remodeling. Frantz and Hofmann (239) note these results expand our current understanding of how different subsets of monocytes infiltrate after myocardial infarction with proinflammatory effects, followed by infiltration of anti-inflammatory monocytes that control repair processes and wound healing. The study by Lee et al. (238) adds another level of complexity, by showing that anti-inflammatory monocytes invade remote regions as well.

Phosphodiesterase-5 inhibitors (PDE5Is) decrease the breakdown of cyclic guanosine monophosphate (cGMP) by PDE5, resulting in higher levels of nitric oxide (NO) to enhance vasodilation (240). In small clinical trials, PDE5I have been effective for treating heart failure with secondary pulmonary arterial hypertension, and is effective in preventing or treating high altitude–associated pulmonary arterial hypertension and pulmonary edema. In pre-clinical studies, inhibiting PDE5, which is specific for cGMP, has found several uses in providing cardioprotective effects in myocardial infarction, doxyrubicin-related cardiomyopathy, and Duchenne muscular dystrophy (241). As the uses for PDE5Is to inhibit cGMP breakdown have expanded, other phosphodiesterases involved in breaking down cyclic adenosine monophosphate (cAMP), such as PDE4, may provide a useful target. Molina et al. (242) studied PDE4, which is expressed in human atrial myocytes and contributes to 15% of the total PDE activity, with PDE4D as the major subtype. Inhibiting PDE4 increased cAMP and L-type calcium currents, and reduced arrhythmias induced by beta-adrenergic receptor stimulation. PDE4 activity was lower in right atrial tissue from patients with permanent atrial fibrillation and heart failure. It was proposed that PDE4 may represent a unique target for atrial arrhythmias. Van Wagoner and Lindsay (243) found these results were intriguing, as a potential additional approach managing atrial fibrillation (AF), the most common arrhythmia.

An attractive treatment strategy is to find effective drugs that may have beneficial off-target effects as well. Matsubara et al. (244) examined this possibility with des-fluoro sitagliptin (DFS), a dipeptidyl peptidase-4 inhibitor that improves glucose metabolism by increasing glucagon-like peptide (GLP)-1, which is used clinically to treat diabetes. They found that DFS decreased atherosclerosis in apolipoprotein-E–deficient mice fed a high-fat diet for 16 weeks,

JACC Vol. 61, No. 3, 2013
January 22, 2013:357–85

which was associated with improved endothelial function in aortic rings. In vitro, DFS decreased inflammation in cultured human macrophages by increasing GLP-1. In a human study, GLP-1 levels were lower in 100 patients with CAD compared with 100 subjects without CAD. It was proposed that DFS, used to treat diabetes, also may have antiatherogenic effects by inhibiting macrophages and improving endothelial function.

Murohara (245) commented on the advantages of incretin-related drugs such as DFS, which increase GLP-1 to reduce blood glucose levels without a high risk for inducing hypoglycemia. DFS attenuated the release of inflammatory cytokines from macrophages by a GLP-1–mediated pathway; others have shown that GLP-1 analogues can decrease macrophage infiltration to inhibit atherosclerosis.

A review by Marzilli et al. (246) challenges conventional wisdom about the nature of chronic ischemic coronary disease, suggesting that inflammation and abnormalities of the microvasculature and the myocardium play important roles in the pathogenesis of this disease. The authors make the case that epicardial stenoses have received excessive attention as the cause for ischemic events and suggest that ongoing efforts must address these other causes. This is a radical hypothesis that may just be correct.

A study by Patel et al. (247) demonstrates that obtaining a pre-hospital ECG by emergency responders slightly prolongs the time at the scene in patients with chest pain (by a few seconds), but actually reduces the time needed to reach the hospital in STEMI patients (by several minutes). This study, conducted in more than 21,000 chest pain patients makes a strong case for routine use of a pre-hospital ECG by first responders.

A study by Hannan et al. (248) compared the appropriateness of bypass surgery (CABG) and PCI in patients with stable coronary symptoms studied through the New York State Reporting System. More than 90% of the CABG patients met current appropriateness guidelines, and only 1.1% were deemed inappropriate. For PCI, only 36.1% were deemed appropriate, 14.3% were inappropriate, and 49.6% of patients had uncertain indications for the procedure.

A paper by Tsimikas et al. (249) demonstrates that the ratio of oxidized phospholipids/apolipoprotein B confers an increased risk of major adverse cardiovascular outcomes during 15 years of follow up. For the highest tertile, this biomarker confers a hazard ratio of 2.4 for CVD and 3.6 for stroke. These data demonstrate the pathophysiological importance of oxidized lipids and suggest that the ratio might be useful in reclassifying individuals into higher- or lower-risk categories.

Valvular heart disease. Recently a new syndrome of AS characterized by severe obstruction with a low gradient and a low-flow state despite preserved left ventricular ejection fraction has been recognized. Clavelet al. (250) studied the outcome of 187 such patients matched with a similar number of patients with either moderate or severe AS with a high gradient. They observed that the prognosis of the patients with paradoxical low-flow, low-gradient severe AS was worse than those with either of the other 2 presentations, emphasizing the importance of properly identifying this cohort of patients. In an accompanying editorial, Baumgartner (251) points out that low-flow, low-gradient aortic stenosis remains a paradoxical and challenging condition, but that mounting evidence supports its existence and the need to treat it aggressively.

Two *Journal* papers dealt with conditions associated with AS. Capoulade et al. (252) reported on the impact of metabolic syndrome on the progression of AS. In 243 patients, metabolic syndrome accelerated the progression of obstruction, a phenomenon most significant in younger individuals and patients receiving statin therapy. These findings highlight the importance of treating metabolic syndrome in AS patients. Aksoy et al. (253) studied whether bisphosphonates, drugs that have been shown to inhibit vascular calcification, slow the progression of AS. They examined 800 women followed for an average of 5 years, using echocardiography. Patients taking biphosphonates did not exhibit any difference in the rate of change of aortic valve area or gradient or survival or freedom from aortic valve replacement compared with those not taking the agent.

Lancellotti et al. (254) examined the clinical outcomes in patients with asymptomatic severe AS classified by transvalvular flow rates and pressure gradients. They observed that patients with low-flow states had impaired prognosis, independent of the gradient. The greatest hazard ratio (5.26) existed for low-flow, low-gradient aortic stenosis. In an accompanying editorial, Flachskampf and Kavianipour (255) point out that low stroke volume is an adverse prognostic sign in aortic stenosis, and also that this study confirms the low incidence in sudden death in these patients. In the same vein, a study by Henkel et al. (256) examined the fate of patients with severe AS and asymptomatic left ventricular systolic dysfunction. They found that this condition was extremely rare, amounting to just 0.4%, but that patients with this condition did not do well with either medical or surgical therapy.

Regarding the therapy of bioprosthetic valves, Brennan et al. (257) studied whether anticoagulation in the first 3 months following bioprosthetic aortic valve implantation was of value. They compared therapy with aspirin only, warfarin only, or a combination of agents in 25,656 patients. The most important finding of their study was that death and embolic events were extremely rare in the first 3 months following bioprosthetic aortic valve replacement. Although the combination of warfarin plus aspirin was associated with reduced risk of death and embolic events, it was associated with an increased risk of bleeding. In an accompanying editorial, Whitlock and Eikelboom (258) point out that the antithrombotic treatment after bioprosthetic aortic valve replacement is uncertain, that these data show that the incidence of adverse events are very low and that warfarin

has no advantage over aspirin, and finally suggest that the combination of warfarin and aspirin be used primarily in those patients at highest risk of thromboembolic events. In another article, Whitlow et al. (259) reported the 12-month results of catheter-based mitral valve leaflet repair with MitraClip (Abbott Vascular, Santa Clara, California) from the EVEREST II trial (Endovascular Valve Edge-to-Edge Repair) high-risk study. The MitraClip device reduced mitral regurgitation in the majority of patients deemed at high risk of surgery, resulting in improved clinical symptoms and significant left ventricular reverse remodeling over 12 months. In an accompanying editorial, Turi and Rosenbloom (260) caution that the results of this trial cannot be extrapolated readily to routine use of MitraClip for high-risk patients. However, given the fact that patients exist with severe mitral regurgitation and no other alternative, they recommend that it be made available.

Whether pregnancy influences the durability of human aortic valve substitutes was evaluated from a retrospective registry; in 31 patients with 55 pregnancies, it was shown that the durability of homograft (n = 13) or autograft (n = 18) prostheses was not affected by pregnancy (261).

Reprint requests and correspondence: Dr. Anthony N. DeMaria, Cardiology Division, UCSD School of Medicine, 3655 Nobel Drive, Suite 630, San Diego, California 92122. E-mail: ademaria@acc.org.

REFERENCES

1. Genereux P, Head SJ, Van Mieghem NM, et al. Clinical outcomes after transcatheter aortic valve replacement using valve academic research consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. J Am Coll Cardiol 2012;59:2317–26.
2. Sinning JM, Hammerstingl C, Vasa-Nicotera M, et al. Aortic regurgitation index defines severity of peri-prosthetic regurgitation and predicts outcome in patients after transcatheter aortic valve implantation. J Am Coll Cardiol 2012;59:1134–41.
3. Urena M, Mok M, Serra V, et al. Predictive factors and long-term clinical consequences of persistent left bundle branch block following transcatheter aortic valve implantation with a balloon-expandable valve. J Am Coll Cardiol 2012;60:1743–52.
4. Unbehaun A, Pasic M, Dreysse S, et al. Transapical aortic valve implantation: incidence and predictors of paravalvular leakage and transvalvular regurgitation in a series of 358 patients. J Am Coll Cardiol 2012;59:211–21.
5. Toggweiler S, Gurvitch R, Leipsic J, et al. Percutaneous aortic valve replacement: vascular outcomes with a fully percutaneous procedure. J Am Coll Cardiol 2012;59:113–8.
6. Toggweiler S, Boone RH, Rodes-Cabau J, et al. Transcatheter aortic valve replacement: outcomes of patients with moderate or severe mitral regurgitation. J Am Coll Cardiol 2012;59:2068–74.
7. Hayashida K, Morice MC, Chevalier B, et al. Sex-related differences in clinical presentation and outcome of transcatheter aortic valve implantation for severe aortic stenosis. J Am Coll Cardiol 2012;59:566–71.
8. Humphries KH, Toggweiler S, Rodes-Cabau J, et al. Sex differences in mortality after transcatheter aortic valve replacement for severe aortic stenosis. J Am Coll Cardiol 2012;60:882–6.
9. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic valve replacement in high risk patients. N Engl J Med 2011;365:2187–98.
10. Reynolds MR, Magnuson EA, Wang K, et al. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis. J Am Coll Cardiol 2012;60:548–58.
11. Genereux P, Webb JG, Svensson LG, et al. Vascular complications after transcatheter aortic valve replacement. J Am Coll Cardiol 2012;60:1043–52.
12. Kappetein AP, Head SJ, Genereux P, t al. Updated standardized endpoint definitions for transcatheter aortic valve implantation. J Am Coll Cardiol 2012;60:1438–54.
13. Hamdan A, Guetta V, Konen E, et al. Deformation dynamics and mechanical properties of the aortic annulus by 4-dimensional computed tomography. J Am Coll Cardiol 2012;59:119–27.
14. Jilaihawi H, Kashif M, Fontana G, et al. Cross-sectional computed tomographic assessment improves accuracy of aortic annular sizing for transcatheter aortic valve replacement and reduces the incidence of paravalvular aortic regurgitation. J Am Coll Cardiol 2012;59:1275–86.
15. Willson AB, Webb JG, LaBounty TM, et al. 3-dimensional aortic annular assessment by multidetector computed tomography predicts moderate or severe paravalvular regurgitation after transcatheter aortic valve replacement. J Am Coll Cardiol 2012;59:1287–94.
16. Amat-Santos IJ, Rodes-Cabau J, Urena M, D et al. Incidence, predictive factors, and prognostic value of new-onset atrial fibrillation following transcatheter aortic valve implantation. J Am Coll Cardiol 2012;59:178–88.
17. von Birgelen C, Basalus MW, Tandjung K, et al. A randomized controlled trial in second-generation zotarolimus-eluting Resolute stents versus everolimus-eluting Xience V stents in real-world patients: the TWENTE trial. J Am Coll Cardiol 2012;59:1350–61.
18. Jensen LO, Thayssen P, Christiansen EH, et al.2-year patient-related versus stent-related outcomes: the SORT OUT IV (Scandinavian Organization for Randomized Trials With Clinical Outcome IV) trial. J Am Coll Cardiol 2012;60:1140–7.
19. Song HG, Park DW, Kim YH, et al. Randomized trial of optimal treatment strategies for in-stent restenosis after drug-eluting stent implantation. J Am Coll Cardiol 2012;59:1093–100.
20. Wohrle J, Zadura M, Mobius-Winkler S, et al. SeQuent Please World Wide Registry: clinical results of SeQuent Please paclitaxel-coated balloon angioplasty in a large-scale, prospective registry study. J Am Coll Cardiol 2012;60:1733–8.
21. Rittger H, Brachmann J, Sinha AM, et al. A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: the PEPCAD-DES study. J Am Coll Cardiol 2012;59:1377–82.
22. Belkacemi A, Agostoni P, Nathoe HM, et al. First results of the DEB-AMI (drug eluting balloon in acute ST-segment elevation MI) trial: a multicenter randomized comparison of drug-eluting balloon plus bare-metal stent versus bare-metal stent versus drug-eluting stent in primary percutaneous coronary intervention with 6-month angiographic, intravascular, functional, and clinical outcomes. J Am Coll Cardiol 2012;59:2327–37.
23. Meredith IT, Verheye S, Dubois CL, et al. Primary endpoint results of the EVOLVE trial: a randomized evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent. J Am Coll Cardiol 2012;59:1362–70.
24. Hofma SH, Brouwer J, Velders MA, et al.Second-generation everolimus-eluting stents versus first-generation sirolimus-eluting stents in acute MI: 1-year results of the randomized XAMI (XienceV Stent vs. Cypher Stent in Primary PCI for Acute MI) trial. J Am Coll Cardiol 2012;60:381–7.
25. Brennan JM, Dai D, Patel MR, et al. Characteristics and long-term outcomes of percutaneous revascularization of unprotected left main coronary artery stenosis in the United States: a report from the National Cardiovascular Data Registry, 2004 to 2008. J Am Coll Cardiol 2012;59:648–54.
26. Park SJ, Kang SJ, Virmani R, Nakano M, Ueda Y. In-stent neoatherosclerosis: a final common pathway of late stent failure. J Am Coll Cardiol 2012;59:2051–7.
27. Le May MR, Wells GA, So DY, et al. Reduction in mortality as a result of direct transport from the field to a receiving center for primary percutaneous coronary intervention. JAm Coll Cardiol 2012;60:1223–30.
28. Mehta SR, Jolly SS, Cairns J, et al., RIVAL Investigators. Effects of radial versus femoral artery access in patients with acute coronary

syndromes with or without ST-segment elevation. J Am Coll Cardiol 2012;60:2490–9.
29. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. J Am Coll Cardiol 2012;60:2481–9.
30. Bertrand OF, Patel T. Radial approach for primary PCI: ready for prime time? J Am Coll Cardiol 2012;60:2500–3.
31. Tearney GJ, Regar E, Akasaka T, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. J Am Coll Cardiol 2012;59: 1058–72.
32. Gonzalo N, Escaned J, Alfonso F, et al. Morphometric assessment of coronary stenosis relevance with optical coherence tomography: a comparison with fractional flow reserve and intravascular ultrasound. J Am Coll Cardiol 2012;59:1080–9.
33. Alfonso F, Paulo M, Gonzalo N, et al. Diagnosis of spontaneous coronary artery dissection by optical coherence tomography. J Am Coll Cardiol 2012;59:1073–9.
34. Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. J Am Coll Cardiol 2012;59:1392–402.
35. McKenney JM, Koren MJ, Kereiakes DJ, Hanotin C, Ferrand AC, Stein EA. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/ REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. J Am Coll Cardiol 2012;59: 2344–53.
36. Melone M, Wilsie L, Palyha O, Strack A, Rashid S. Discovery of a new role of human resistin in hepatocyte low-density lipoprotein receptor suppression mediated in part by proprotein convertase subtilisin/kexin type 9. J Am Coll Cardiol 2012;59:1697–705.
37. Magnussen CG, Koskinen J, Juonala M, et al. A diagnosis of the metabolic syndrome in youth that resolves by adult life is associated with a normalization of high carotid intima-media thickness and type 2 diabetes mellitus risk: the Bogalusa Heart and Cardiovascular Risk in Young Finns studies. J Am Coll Cardiol 2012;60:1631–9.
38. Mackey RH, Greenland P, Goff DC, Lloyd-Jones D, Sibley CT, Mora S. High-density lipoprotein cholesterol and particle concentrations, carotid atherosclerosis and coronary events. J Am Coll Cardiol 2012;60:508–16.
39. deGoma EM, Rader DJ. High-density lipoprotein particle number: a better measure to quantify high-density lipoprotein? J Am Coll Cardiol 2012;60:517–20.
40. Lazzaretti RK, Kuhmmer R, Sprinz E, Polanczyk CA, Ribeiro JP. Dietary intervention prevents dyslipidemia associated with highly active antiretroviral therapy in human immunodeficiency virus type 1-infected individuals. J Am Coll Cardiol 2012;59:979–88.
41. Stein JH. Nutritional therapy to prevent dyslipidemia in patients starting antiretroviral therapy for human immunodeficiency virus. J Am Coll Cardiol 2012;59:989–90.
42. Brandt MC, Mahfoud F, Reda S, et al. Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. J Am Coll Cardiol 2012;59:901–9.
43. Banerjee S, Das TS, Abu-Fadel MS, et al. Pilot trial of cryoplasty or conventional balloon post-dilation of nitinol stents for revascularization of peripheral arterial segments: the COBRA trial. J Am Coll Cardiol 2012;60:1352–9.
44. Rastan A, Brechtel K, Krankenberg H, et al. Sirolimus-eluting stents for treatment of infrapopliteal arteries reduce clinical event rate compared to bare-metal stents: long-term results from a randomized trial. J Am Coll Cardiol 2012;60:587–91.
45. Bijuklic K, Wandler A, Hazizi F, Schofer J. The PROFI study (Prevention of Cerebral Embolization by Proximal Balloon Occlusion Compared to Filter Protection During Carotid Artery Stenting): a prospective randomized trial. J Am Coll Cardiol 2012;59:1383–9.
46. Hawkins BM, Kennedy KF, Giri J, et al. Pre-procedural risk quantification for carotid stenting using the CAS score: a report from the NCDR CARE Registry. J Am Coll Cardiol 2012 60:1617–22.
47. Gress DR. The problem with asymptomatic cerebral embolic complications in vascular procedures: what if they are not asymptomatic? J Am Coll Cardiol 2012 60:1614–6.
48. Lu Q, Feng J, Zhou J, et al. Endovascular repair of ascending aortic dissection: a novel treatment option for patients judged unfit for direct surgical repair. J Am Coll Cardiol 2012 Oct 20 [E-pub ahead of print].
49. Stabile E, Virga V, Salemme L, et al. Drug-eluting balloon for treatment of superficial femoral artery in-stent restenosis. J Am Coll Cardiol 2012;60:1739–42.
50. Scheinert D, Katsanos K, Zeller T, et al., and the ACHILLES Investigators. A prospective randomized multicenter comparison of balloon angioplasty and infrapopliteal stenting with the sirolimus-eluting stent in patients with ischemic peripheral arterial disease: one year results from the ACHILLES trial. J Am Coll Cardiol 2012;60: 2290–5.
51. Rogers JH, Goldstein I, Kandzari DE,et al. Zotarolimus-eluting peripheral stents for the treatment of erectile dysfunction in subjects with suboptimal response to phosdodiesterase-5 inhibitors. J Am Coll Cardiol 2012;60:2618–27.
52. Shishehbor MH, Philip F. Endovascular treatment for erectile dysfunction: an old paradigm revisited. J Am Coll Cardiol 2012;60: 2628–30.
53. Kim B-K, Hong M-K, Shin D-H, et al. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). J Am Coll Cardiol 2012;60:1340–8.
54. Ferreira-González I, Marsal JR, Ribera A, et al. Double antiplatelet therapy after drug-eluting stent implantation: risk associated with discontinuation within the first year. J Am Coll Cardiol 2012;60: 1333–9.
55. Sibbing D, Bernlochner I, Schulz S, et al.Prognostic Value of a high on-clopidogrel treatment platelet reactivity in bivalirudin versus abciximab treated non–ST-segment elevation MI patients: ISAR-REACT 4 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment-4) Platelet Substudy. J Am Coll Cardiol 2012;60:369–77.
56. Alexopoulos D, Galati A, Xanthopoulou I, et al. Ticagrelor versus prasugrel in acute coronary syndrome patients with high on-clopidogrel platelet reactivity following percutaneous coronary intervention: a pharmacodynamic study. J Am Coll Cardiol 2012;60: 193–9.
57. Price MJ, Murray SS, Angiolillo DJ, et al. Influence of genetic polymorphisms on the effect of high- and standard-dose clopidogrel after percutaneous coronary intervention: the GIFT (Genotype Information and Functional Testing) study. J Am Coll Cardiol 2012; 59:1928–37.
58. Frelinger AL, Lee RD, Mulford DJ,et al. A randomized, 2-period, crossover design study to assess the effects of dexlansoprazole, lansoprazole, esomeprazole, and omeprazole on the steady-state pharmacokinetics and pharmacodynamics of clopidogrel in healthy volunteers. J Am Coll Cardiol 2012;59:1304–11.
59. Smith PK, Goodnough LT, Levy JH, et al. Mortality benefit with prasugrel I the TRITON-TIMI 38 coronary artery bypass grafting cohort: risk-adjusted retrospective data analysis. J Am Coll Cardiol 2012;60:388–96.
60. Trenk D, Stone GW, Gawaz M, et al. A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents. J Am Coll Cardiol 2012;59: 2159–64.
61. Price MJ, Walder JS, Baker BA, et al. Recovery of platelet function after discontinuation of a prasugrel or clopidogrel maintenance dosing in aspirin-treated patients with stable coronary disease. J Am Coll Cardiol 2012;59:2338–43.
62. Tello-Montoliu A, Tomasello SD, Ferreiro JL,et al Pharmacodynamic effects of prasugrel dosing regimens in patients on maintenance prasugrel therapy. J Am Coll Cardiol 2012;59:1681–7.
63. Sachdeva A, Bavisetty S, Beckham G, et al. Discontinuation of long-term clopidogrel therapy is associated with death and myocar-

dial infarction after saphenous vein graft percutaneous coronary intervention. J Am Coll Cardiol 2012;60:2357–63.
64. Erlinge D, Ten Berg J, Foley D, et al. Reduction in platelet reactivity with prasugrel 5 mg in low-body-weight patients is noninferior to prasugrel 10 mg in higher-body-weight patients: results from the FEATHER trial. J Am Coll Cardiol 2012;60:2032–40.
65. Singla S, Sachdeva R, Uretsky BF. The risk of adverse cardiac and bleeding events following noncardiac surgery relative to antiplatelet therapy in patients with prior percutaneous coronary intervention. J Am Coll Cardiol 2012;60:2005–16.
66. Lip GYH, Larsen TB, Skjoth F, Rasmussen LH. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. J Am Coll Cardiol 2012;60:738–46.
67. Cannon CP, Kohli P. Danger ahead: watch out for indirect comparisons! J Am Coll Cardiol 2012; 60:747–8.
68. Apostolakis S, Lane DA, Guo Y, Buller H, Lip GYH. Performance of the $HEMORR_2HAGES$, ATRIA, and HAS-BLED Bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation. J Am Coll Cardiol 2012;60:861–7.
69. Price J, Hynes M, Labinaz M, Puel M, Boodhwani M. Mechanical valve thrombosis with dabigatran. J Am Coll Cardiol 2012;60: 1710–1.
70. Vardeny O, Wu DH, Desai A, et al., RALES Investigators. Influence of baseline and worsening renal function on efficacy of spironolactone in patients with severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). J Am Coll Cardiol 2012;60:2082–9.
71. Kiernan MS, Konstam MA. Moderate renal insufficiency does not attenuate the clinical benefit of aldosterone antagonists in heart failure. J Am Coll Cardiol 2012; 60:2090–1.
72. Chen HH, Glockner JF, Schirger JA, Cataliotti A, Redfield MM, Burnett JC Jr. Novel protein therapeutics for systolic heart failure: chronic subcutaneous b-type natriuretic peptide. J Am Coll Cardiol 2012;60:2305–12.
73. Ahmad T, Felker GM. Subcutaneous B-type natriuretic peptide for treatment of heart failure: a dying therapy reborn? J Am Coll Cardiol 2012;60:2313–5.
74. Chen J, Long JB, Hurria A, Owusu C, Steingart RM, Gross CP. Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. J Am Coll Cardiol 2012;60: 2504–12.
75. Lenihan D. Progression of heart failure from AHA/ACC stage A to stage B or even C: can we all agree we should try to prevent this from happening? J Am Coll Cardiol 2012;60:2513–4.
76. Seicean S, Seicean A, Plana JC, Budd GT, Marwick TH. Effect of statin therapy on the risk of incident heart failure in breast cancer patients receivining anthracycline chemotherapy: an observational clinical cohort study. J Am Coll Cardiol 2012 60:2384–90.
77. Lenihan D. Statins in preparation for chemotherapy: "do these medications help your fitness for battle?" J Am Coll Cardiol 2012; 60:2391–2.
78. Terrovitis JV, Kaldara E, Ntalianis A, et al. Intravenous iron alone is equally effective with the combination of iron and erythropoietin for the treatment of iron-deficiency anemia in advanced heart failure. J Am Coll Cardiol 2012;60:2255–6.
79. Forman DE, Fleg JL, Kitzman DW, et al.6-minute walk test provides prognostic utility comparable to cardiopulmonary exercise testing in ambulatory outpatients with systolic heart failure. J Am Coll Cardiol 2012;60:2653–61.
80. Spruit MA, Maeder MT, Knackstedt C, et al., TIME-CHF Investigators. Prognostic value of self-reported versus objectively measured functional capacity in patients with heart failure: results from the TIME-CHF (Trial of Intensified Versus Standard Medical Therapy in Elderly Patients With Congestive Heart Failure). J Am Coll Cardiol 2012;60:2125–6.
81. Khan FZ, Virdee MS, Palmer CR, et al. Targeted left ventricular lead placement to guide cardiac resynchronization therapy. J Am Coll Cardiol 2012;59:1509–18.
82. Ghali JK. The next frontier of clinical trials. J Am Coll Cardiol 2012;59:1519–20.
83. Swedberg K, Komajda M, Bohm M, et al. Effects on outcomes of heart rate reduction by ivabradine in patients with congestive heart failure: is there an influence of beta-blocker dose? J Am Coll Cardiol 2012;59;1938–45.
84. Sarraf M, Francis GS. It is all about heart rate. or is it? J Am Coll Cardiol 2012;59:1946–7.
85. Uriel N, Morrison KA, Garan AR, et al. Development of a novel echocardiography ramp test for speed optimization and diagnosis of device thrombosis in continuous-flow left ventricular assist devices. J Am Coll Cardiol 2012;60;1764–75.
86. Rogers JG, Milano CA. Ramping up evidence-based ventricular assist device care. J Am Coll Cardiol 2012;60:1776–7.
87. Priori SE, Gasparini M, Napolitano C, et al Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. J Am Coll Cardiol 2012;59:37–45.
88. Brignole M, Occhetta E, Bongiorni MG, et al., SAFE-ICD Study Investigators. Clinical evaluation of defibrillation testing in an unselected population of 2,120 consecutive patients undergoing first implantable cardioverter-defibrillator implant. J Am Coll Cardiol 2012;60:981–7.
89. Estes NA. Defibrillation testing: should the paradigm shift? J Am Coll Cardiol 2012; 60:988–9.
90. Ganesan AN, Brooks AG, Roberts-Thomson KC, Lau DH, Kalman JM, Sanders P. Role of AV nodal ablation in cardiac resynchronization in patients with coexistent atrial fibrillation and heart failure a systematic review. J Am Coll Cardiol 2012;59:719–26.
91. Gasparini M, Galimberti P. AV junction ablation in heart failure patients with atrial fribrillation treated with cardiac resynchronization therapy: the picture is now clear! J Am Coll Cardiol 2012;59:727–9.
92. Olde Nordkamp LR, Dabriri Abkenari L, Boersma LV, et al. AV junction ablation in heart failure patients with atrial fribrillation treated with cardiac resynchronization therapy: the picture is now clear. J Am Coll Cardiol 2012;60:1933–9.
93. Miyasaka Y, Barnes M, Bailey K, et al. Mortality trends in patients diagnosed with first atrial fibrillation a 21-year community-based study. J Am Coll Cardiol 2007;49:986–92.
94. Swartz MF, Fink GW, Sarwar MF, et al. n. J Am Coll Cardiol 2012;60:1799–806.
95. Mahnkopf C, Badger TJ, Burgon NS, et al. Evaluation of the left atrial substrate in patients with lone atrial fibrillation using delayed-enhanced MRI: implications for disease progression and response to catheter ablation. Heart Rhythm 2010;7:1475–81.
96. Lalani G, Schricker A, Gibson M, Rostamanian A, Krummen DE, Narayan SM. Atrial conduction slows immediately before the onset of human atrial fibrillation: a bi-atrial contact mapping study of transitions to atrial fibrillation. J Am Coll Cardiol 2012;59:595–606.
97. Narayan SM, Krummen DE, Shivkumar K, Clopton P, Rappel W-J, Miller J. Treatment of atrial fibrillation by the ablation of localized sources: the Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation: CONFIRM tial. J Am Coll Cardiol 2012;60:628–36.
98. Stiles MK, John B, Wong CX, et al. Paroxysmal lone atrial fibrillation is associated with an abnormal atrial substrate: characterizing the "second factor". J Am Coll Cardiol 2009;53:1182–91.
99. Deftereos S, Giannopoulos G, Kossyvakis C, et al. Colchicine for prevention of early atrial fibrillation recurrence after pulmonary vein isolation: a randomized controlled study. J Am Coll Cardiol 2012; 60:1790–6.
100. Marcus GM, Hsu JC. Colchicine after pulmonary vein isolation to prevent the early recurrence of atrial fibrillation: mollifying an inflammatory response? J Am Coll Cardiol 2012;60:1797–8.
101. Sawhney N, Anousheh R, Chen WC, Narayan S, Feld GK. Five-year outcomes after segmental pulmonary vein isolation for paroxysmal atrial fibrillation. Am J Cardiol 2009;104:366–72.
102. Calkins CH.2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Heart Rhythm 2012;9:632–96.
103. Nielsen JC, Johannessen A, Raatikainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. New Engl J Med 2012;367:1587–95.
104. Ellis ER, Culler SD, Simon AW, Reynolds MR. Trends in utilization and complications of catheter ablation for atrial fibrillation in Medicare beneficiaries. Heart Rhythm 2009;6:1267–73.

105. Shivkumar K, Ellenbogen K, Hummel JD, Miller JM, Steinberg JS. Acute termination of human atrial fibrillation by identification and catheter ablation of localized rotors and sources: first multicenter experience of focal impulse and rotor modulation (FIRM) ablation. J Cardiovasc Electrophysiol 2012 Aug 29 [E-pub ahead of print].
106. Pokushalov E, Romanov A, Corbucci G, et al. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. J Am Coll Cardiol 2012;60:1163–70.
107. Verma A, Kilicaslan F, Pisano E, et al. Response of atrial fibrillation to pulmonary vein antrum isolation is directly related to resumption and delay of pulmonary vein conduction. Circulation 2005;112: 627–35.
108. Ouyang F, Antz M, Ernst S, et al. Recovered Pulmonary Vein Conduction as a Dominant Factor for Recurrent Atrial Tachyarrhythmias After Complete Circular Isolation of the Pulmonary Veins: Lessons From Double Lasso Technique. Circulation 2005; 111:127–35.
109. Pratola C, Baldo E, Notarstefano P, Toselli T, Ferrari R. Radiofrequency ablation of atrial fibrillation: is the persistence of all intraprocedural targets necessary for long-term maintenance of sinus rhythm? Circulation 2008;117:136–43.
110. Kowalski M, Grimes MM, Perez FJ, et al. Histopathologic characterization of chronic radiofrequency ablation lesions for pulmonary vein isolation. J Am Coll Cardiol 2012;59:930–8.
111. Pison L, La Meir M, van Opstal J, Blaauw Y, Maessen J, Crijns HJ. Hybrid thoracoscopic surgical and transvenous catheter ablation of atrial fibrillation. J Am Coll Cardiol 2012;60:54–61.
112. Calkins H. Hybrid thoracoscopic and transvenous catheter ablation of atrial fibrillation: is this the answer we are searching for? J Am Coll Cardiol 2012;60:62–3.
113. Mohanty S, Mohanty P, Di Biase L, et al. Impact of metabolic syndrome on procedural outcomes in patients with atrial fibrillation undergoing catheter ablation. J Am Coll Cardiol 2012;59:1295–301.
114. Munger TM, Dong YX, Masaki M, et al. Electrophysiological and hemodynamic characteristics associated with obesity in patients with atrial fibrillation. J Am Coll Cardiol 2012;60:851–60.
115. Shah RU, Freeman JV, Shilane D, Wang PJ, Go AS, Hlatky MA. Procedural Complications, Rehospitalizations, and Repeat Procedures After Catheter Ablation for Atrial Fibrillation. J Am Coll Cardiol 2012;59:143–9. Erratum in: J Am Coll Cardiol 2012;59: 1492.
116. Flaker G, Ezekowitz M, Yusuf S, et al. Efficacy and safety of dabigatran compared to warfarin in patients with paroxysmal, persistent, and permanent atrial fibrillation: results from the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) study. J Am Coll Cardiol 2012;59:854–5.
117. Lakkireddy D, Reddy YM, Di Biase L, et al. Feasibility and safety of dabigatran versus warfarin for periprocedural anticoagulation in patients undergoing radiofrequency ablation for atrial fibrillation: results from a multicenter prospective registry. J Am Coll Cardiol 2012;59:1168–74.
118. Knight BP. Anticoagulation for atrial fibrillation ablation: what is the optimal strategy? J Am Coll Cardiol 2012;59:1175–7.
119. Greener ID, Sasano T, Wan X, et al. Connexin43 gene transfer reduces ventricular tachycardia susceptibility after myocardial infarction. J Am Coll Cardiol 2012;60:1103–10.
120. Saffitz JE, Kleber AG. Gap junctions, slow conduction, and ventricular tachycardia after myocardial infarction. J Am Coll Cardiol 2012;60:1111–3.
121. Di Biase L, Santangeli P, Burkhardt DJ, et al. Endo-epicardial homogenization of the scar versus limited substrate ablation for the treatment of electrical storms in patients with ischemic cardiomyopathy. J Am Coll Cardiol 2012;60:132–41.
122. Shivkumar K, Tung R. Improving our understanding of epicardial ventricular tachycardia in nonischemic cardiomyopathy. J Am Coll Cardiol 2009;54:809–11.
123. Han S, Kobayashi K, Joung B, et al. Electroanatomic remodeling of the left stellate ganglion after myocardial infarction. J Am Coll Cardiol 2012;59:954–61.
124. Nademanee K, Taylor R, Bailey WE, Rieders DE, Kosar EM. Treating electrical storm: sympathetic blockade versus advanced cardiac life support-guided therapy. Circulation 2000;102:742–7.
125. Ajijola OA, Lellouche N, Bourke T, et al. Bilateral cardiac sympathetic denervation for the management of electrical storm. J Am Coll Cardiol 2012;59:91–2.
126. Smedsrud MK, Sarvari S, Haugaa KH, et al. Duration of myocardial early systolic lengthening predicts the presence of significant coronary artery disease. J Am Coll Cardiol 2012;60:1086–93.
127. Tsao CW, Preis SR, Peloso GM, et al. Relations of long-term and contemporary lipid levels and lipid genetic risk score with coronary artery calcium in the Framingham Heart Study. J Am Coll Cardiol 2012;60:2364–71.
128. Hartiala O, Magnussen CG, Kajander S, et al. Adolescence risk factors are predictive of coronary artery calcification at middle age. the Cardiovascular Risk in Young Finns study. J Am Coll Cardiol 2012;60:1364–70.
129. Hecht HS. The child is father of the man. J Am Coll Cardiol 2012;60:1371–3.
130. Chinnaiyan KM, Raff GL, Goraya T, et al., ACIC (Advanced Cardiovascular Imaging Consortium) Coronary computed tomography angiography after stress testing. results from a multicenter, statewide registry. J Am Coll Cardiol 2012;59:688–95.
131. De Feyter PJ, Nieman K. Computed tomography coronary angiography. a noninvasive escape when stress tests fail (caught between guidelines and gut feeling). J Am Coll Cardiol 2012;59:696–7.
132. Cho I, Shim J, Chang H, et al. Prognostic value of multi-detector coronary computed tomograpic angiography in relation to exercise electrocardiogram in patients with suspected coronary artery disease. J Am Coll Cardiol 2012;60:2205–15.
133. Taylor A. Improving the odds in the evaluation of chest pain. J Am Coll Cardiol 2012;60:2216–17.
134. Shaw LJ, Hausleiter J, Achenbach S, et al., for the CONFIRM (Coronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter Registry) investigators. Coronary computed tomographic angiography as a gatekeeper to invasive diagnostic and surgical procedures: results from the Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry. J Am Coll Cardiol 2012 60: 2103–14.
135. Sato A, Nozato T, Hikita H, et al. Prognostic value of myocardial contrast delayed enhancement with 64-slice multidetector computed tomography after acute myocardial infarction. J Am Coll Cardiol 2012;59:730–8.
136. Fukushima K, Bravo PE, Higuchi T, et al. Molecular PET/CT imaging of cardiac angiotensin ii type 1 receptors. J Am Coll Cardiol 2012 60:2527–34.
137. Schindler TH, Dilsizian V. Cardiac PET-CT Imaging of the rennin-angiotensin system in humans holds promise for image-guided approach to heart failure therapy. J Am Coll Cardiol 2012; 60:2535–8.
138. Kim YH, Ahn JM, Park DW, et al. Impact of ischemia-guided revascularization with myocardial perfusion imaging for patients with multivessel coronary disease. J Am Coll Cardiol 2012;60:181–90.
139. Weintraub WS. Should ischemia guide revascularization? J Am Coll Cardiol 2012;60:191–2.
140. Jaarsma C, Leiner T, Bekkers SC, et al. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: a meta-analysis. J Am Coll Cardiol 2012;59: 1719–28.
141. McArdle BA, Dowsley TF, deKemp RA, Wells GA, Beanlands RS. Does rubidium-82 PET have superior accuracy to spect perfusion imaging for the diagnosis of obstructive coronary disease?: a systematic review and meta-analysis. J Am Coll Cardiol 2012;60:1828–37.
142. Morton G, Chiribiri A, Ishida M, et al. Quantification of absolute myocardial perfusion in patients with coronary artery disease: comparison between cardiovascular magnetic resonance and positron emission tomography. J Am Coll Cardiol 2012;60:1546–55.
143. Gerber B. Quantification of myocardial perfusion and myocardial perfusion reserve by positron emission tomography and cardiovascular magnetic resonance imaging. J Am Coll Cardiol 2012;60:1556–7.
144. Jogiya R, Kozerke S, Morton G, et al. Validation of dynamic 3-dimensional whole heart magnetic resonance myocardial perfusion imaging against fractional flow reserve for the detection of significant coronary artery disease. J Am Coll Cardiol 2012;60:756–65.

145. Arnold JR, Karamitsos TD, Bhamra-Ariza P, et al. Myocardial oxygenation in coronary artery disease: insights from blood oxygen level–dependent magnetic resonance imaging at 3 Tesla. J Am Coll Cardiol 2012;59:1954–64.
146. Weinsaft JW, Spincemaille P. BOLD new directions in myocardial ischemia imaging: myocardial oxygenation assessment by cardiac magnetic resonance. J Am Coll Cardiol 2012;59:1965–7.
147. Wu K. Myocardial viability imaging: dead or alive? J Am Coll Cardiol 2012;59:836–7.
148. Gerber BL, Rousseau MF, Ahn SA, et al. Prognostic value of myocardial viability by delayed-enhanced magnetic resonance in patients with coronary artery disease and low ejection fraction: impact of revascularization therapy. J Am Coll Cardiol 2012;59:825–35.
149. Todiere G, Aquaro GD, Piaggi P, et al. Progression of myocardial fibrosis assessed with cardiac magnetic resonance in hypertrophic cardiomyopathy. J Am Coll Cardiol 2012;60:922–9.
150. Bluemke D, Yang E. Hypertrophic cardiomyopathy: refining the lens of cardiac magnetic resonance to evaluate late gadolinium enhancement. J Am Coll Cardiol 2012;60:930–1.
151. Klem I, Weinsaft JW, Bahnson TD, et al. Assessment of myocardial scarring improves risk stratification in patients evaluated for cardiac defibrillator implantation. J Am Coll Cardiol 2012;60:408–20.
152. Mewton N, Chevalier P. Scaring myocardial scars: new targets for the electrical fairy? J Am Coll Cardiol 2012;60:421–2.
153. Hachamovitch R, Nutter B, Hlatky MA, et al., SPARC Investigators. Patient management after noninvasive cardiac imaging results from SPARC (Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease). J Am Coll Cardiol 2012;59:462–74.
154. Einav S, Kaufman N, Algur N, Kark J. Modeling serum biomarrkers S100B and NSE as predictors of outcome following out-of-hospital cardiac arrest: an aid to clinical decision making. J Am Coll Cardiol 2012;60:304–11.
155. Comess KA, Beach KW. Predicting full recovery after out of hospital cardiac arrest. J Am Coll Cardiol 2012;60:312–4.
156. Doehner W, von Haehling S, Suhr J, et al. Elevated plasma levels of neuropeptide proenkephalin a predict morality and functional outcome in ischemic stroke. J Am Coll Cardiol 2012;60:346–54.
157. Zampetaki A, Willeit P, Tilling L, et al. Prospective study on circulating mircoRNAs and risk of myocardial infarction. J Am Coll Cardiol 2012;60:290–9.
158. Engelhardt S. Small RNA biomarkers come of age. J Am Coll Cardiol 2012;60:300–3.
159. Nadir MA, Rekhraj S, Wei L, et al. Improving the primary prevention of cardiovascular events by using biomarkers to identify individuals with silent heart disease. J Am Coll Cardiol 2012;60: 960–8.
160. Richards M. Biomarkers and silent cardiac disease in primary prevention: time to unmask the damage. J Am Coll Cardiol 2012; 60:969–70.
161. Watabe H, Sato A, Akiyama D, et al. Impact of coronary plaque composition on cardiac troponinelevation after percutaneous coronary intervention in stable angina pectoris: a computed tomorgraphy analysis. J Am Coll Cardiol 2012;59:1881–8.
162. Malpeso J, Budoff MJ. Predicting periprocedural myocardial infarction: target-lesion plaque characterization with coronary computed tomography angiography. J Am Coll Cardiol 2012;59:1889–90.
163. Ho JE, Liu C, Lyass A, et al. Galectin-3, a marker of cardiac fibrosis, predicts incident heart falure in the community. J Am Coll Cardiol 2012;60:1249–56.
164. Morrow DA, O'Donoghue ML. Galectin-3 in cardiovascular disease: a possible window into early myocardial fibrosis. J Am Coll Cardiol 2012;60:1257–8.
165. Rubin J, Matsushita K, Ballantyne CM, Hoogeveen R, Coresh J, Selvin E. Chronic hyperglycemia and subclincal myocardial injury. J Am Coll Cardiol 2012;59:484–9.
166. De Lemos JA, Grundy SM. Low levels of circulating troponin as an intermediate phenotype in the pathway to heart failure. J Am Coll Cardiol 2012;59:490–2.
167. Ranthe MF, Carstensen L, Oyen N, et al. Family history of premature death and risk of early-onset cardiovascular disease. J Am Coll Cardiol 2012;60:814–21.
168. Tseng FY, Lin WY, Lin CC, et al. Subclinical hypothyroidism is associated with increased risk of all-cause and cardiovascular mortality in adults. J Am Coll Cardiol 2012;60:730–7.
169. Kostis WJ, Cheng JQ, Dobrzynski JM, Cabrera J, Kostis JB. Meta-analysis of statin effects in women versus men. J Am Coll Cardiol 2012;59:572–82.
170. Mora S, Glynn RJ, Boekholdt M, Nordestgaard BG, Kastelein JJP, Ridker PM. On-treatment non-high-density lipoprotein cholesterol, apolipoprotein b, triglycerides, and lipid ratios in relation to residual vascular risk after treatment with potent statin therapy. J Am Coll Cardiol 2012;59:1521–8.
171. Choudhry NK, Fischer MA, Avorn JL, et al. The impact of reducing cardiovascular medication copayments on health spending and resource utilization. J Am Coll Cardiol 2012;60:1817–24.
172. Wang KL, Liu CJ, Chao TF, et al. Statins, risk of diabetes, and implications on outcomes in the general population. J Am Coll Cardiol 2012;60:1231–8.
173. Blumenthal JA, Sherwood A, Babyak MA, et al. Exercise and pharmacological treatment of depressive symptoms in patients with coronary heart disease. results of the UPBEAT (Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy) study. J Am Coll Cardiol 2012;60:1053–63.
174. Lee DC, Sui X, Church TS, Lavie CJ, Jackson AS, Blair SN. Changes in fitness and fatness on the development of cardiovascular disease risk factors. J Am Coll Cardiol 2012;59:665–72.
175. Lavie CJ, DeSchutter A, Patel DA, Romero-Corral A, Artham SM, Milani RV. Body composition and survival in stable coronary heart disease. impact of lean mass index and body fat in the "obesity paradox." J Am Coll Cardiol 2012;60:1374–80.
176. Geisler BP, Egan BM, Cohen JT, et al. Cost-effectiveness and clinical effectiveness of catheter-based renal denervation for resistant hypertension. J Am Coll Cardiol 2012;60:1271–7.
177. Messenger JC, Ho KKL, Young CH, et al. The National Cardiovascular Data Registry (NCDR) data quality brief. J Am Coll Cardiol 2012;60:1484–8.
178. Guo F, He D, Zhang W, Walton G. Trends in prevalence, awareness, management, and control of hypertension among United States adults, 1999–2010. J Am Coll Cardiol 2012;60:599–606.
179. Duval X, Delahaye F, Alla F, et al. Temporal trends in infective endocarditis in the context of prophylasix guidelines modifications. J Am Coll Cardiol 2012;59:1968–76.
180. Wang A. The changing epidemiology of infective endocarditis. the paradox of prophylaxis in the current and future eras. J Am Coll Cardiol 2012;59:1977–8.
181. Halkin A, Steinvil A, Ross R, Adler A, Rozovski U, Viskin S. Preventing sudden death of athletes with electrocardiographic screening: what is the absolute benefit and how much will it cost? J Am Coll Cardiol 2012;60:2271–6.
182. Pelliccia A. Is the cost the reason for missing the ECG advantages? J Am Coll Cardiol 2012;60:2277–9.
183. Cresci S, Dorn GW 2nd, Jones PG, et al. Adrenergic-pathway gene variants influence beta-blocker-related outcomes after acute coronary syndrome in a race-specific manner. J Am Coll Cardiol 2012;60:898–907.
184. O'Connor CM, Fiuzat M, Carson PE, et al. Combinatorial pharmacogenetic interactions of bucindolol and beta(1), alpha(2c) adrenergic receptor polymorphisms. PloS One 2012;7:e44324.
185. Gudbjartsson DF, Arnar DO, Helgadottir A, et al. Variants conferring risk of atrial fibrillation on chromosome 4q25. Nature 2007;448: 353–7.
186. Kaab S, Darbar D, van Noord C, et al. Large scale replication and meta-analysis of variants on chromosome 4q25 associated with atrial fibrillation. Euro Heart J 2009;30:813–9.
187. Parvez B, Vaglio J, Rowan S, et al. Symptomatic response to antiarrhythmic drug therapy is modulated by a common single nucleotide polymorphism in atrial fibrillation. J Am Coll Cardiol 2012;60:539–45.
188. Daubert JP, Pitt GS. Can polymorphisms predict response to antiarrhythmic drugs in atrial fibrillation? J Am Coll Cardiol 2012; 60:546–7.
189. Ritchie MD, Rowan S, Kucera G, et al. Chromosome 4q25 variants are genetic modifiers of rare ion channel mutations associated with familial atrial fibrillation. J Am Coll Cardiol 2012;60:1173–81.

190. Judge DP. The complex genetics of atrial fibrillation. J Am Coll Cardiol 2012;60:1182–4.
191. Jamshidi Y, Nolte IM, Dalageorgou C, et al. Common variation in the NOS1AP gene is associated with drug-induced QT prolongation and ventricular arrhythmia. J Am Coll Cardiol 2012;60:841–50.
192. Arking DE, Pfeufer A, Post W, et al. A common genetic variant in the NOS1 regulator NOS1AP modulates cardiac repolarization. Nat Genet 2006;38:644–51.
193. Eijgelsheim M, Aarnoudse AL, Rivadeneira F, et al. Identification of a common variant at the NOS1AP locus strongly associated to QT-interval duration. Hum Mol Genet 2009;18:347–57.
194. Newton-Cheh C, Eijgelsheim M, Rice KM, et al. Common variants at ten loci influence QT interval duration in the QTGEN Study. Nat Genet 2009;41:399–406.
195. Mann SA, Otway R, Guo G, et al. Epistatic effects of potassium channel variation on cardiac repolarization and atrial fibrillation risk. J Am Coll Cardiol 2012;59:1017–25.
196. Scanu AM, Lawn RM, Berg K. Lipoprotein(a) and atherosclerosis. Ann Intern Med 1991;115:209–18.
197. Helgadottir A, Gretarsdottir S, Thorleifsson G, et al. Apolipoprotein(a) genetic sequence variants associated with systemic atherosclerosis and coronary atherosclerotic burden but not with venous thromboembolism. J Am Coll Cardiol 2012;60:722–9.
198. Tsimikas S, Hall JL. Lipoprotein(a) as a potential causal genetic risk factor of cardiovascular disease: a rationale for increased efforts to understand its pathophysiology and develop targeted therapies. J Am Coll Cardiol 2012;60:716–21.
199. Crotti L, Marcou CA, Tester DJ, et al.Spectrum and prevalence of mutations involving brs1- through brs12-susceptibility genes in a cohort of unrelated patients referred for brugada syndrome genetic testing: implications for genetic testing. J Am Coll Cardiol 2012;60:1410–8.
200. Kaufman ES. Genetic testing in brugada syndrome. J Am Coll Cardiol 2012;60:1419–20.
201. Barbato E, Bartunek J, Mangiacapra F, et al. Influence of rs5065 atrial natriuretic peptide gene variant on coronary artery disease. J Am Coll Cardiol 2012;59:1763–70.
202. Mann SA, Castro ML, Ohanian M, et al. R222Q SCN5A mutation is associated with reversible ventricular ectopy and dilated cardiomyopathy. J Am Coll Cardiol 2012;60:1566–73.
203. Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. J Am Coll Cardiol 2012;60:705–15.
204. van Rijsingen IA, Arbustini E, Elliott PM, et al. Risk factors for malignant ventricular arrhythmias in Lamin A/C mutation carriers: a European cohort study. J Am Coll Cardiol 2012;59:493–500.
205. Maron BJ, Semsarian C. Prevention of sudden death for patients with cardiomyopathies another step forward. J Am Coll Cardiol 2012;59:501–2.
206. Raeis-Dauve V, Philip-Couderc P, Faggian G, et al. Increased expression of adenosine triphosphate-sensitive K+ channels in mitral dysfunction: mechanically stimulated transcription and hypoxia-induced protein stability? J Am Coll Cardiol 2012;59:390–6.
207. Lopaschuk GD, Jaswal JS. Hypoxia-induced adaptation to mitral regurgitation: a role for K ATP channel up-regulation? J Am Coll Cardiol 2012;59:397–9.
208. Das D, Gawdzik J, Dellefave-Castillo L, et al. S100A12 expression in thoracic aortic aneurysm is associated with increased risk of dissection and perioperative complications. J Am Coll Cardiol 2012;60:775–85.
209. Banka CL. On male-specific estrogen action: good for the gander? J Am Coll Cardiol 2012;59:418–9.
210. Kararigas G, Bito V, Tinel H, et al. Transcriptome characterization of estrogen-treated human myocardium identifies myosin regulatory light chain interacting protein as a sex-specific element influencing contractile function. J Am Coll Cardiol 2012;59:410–7.
211. Benn M, Tybjaerg-Hansen A, McCarthy MI, Jensen GB, Grande P, Nordestgaard BG. Nonfasting glucose, ischemic heart disease, and myocardial infarction: a Mendelian randomization study. J Am Coll Cardiol 2012;59:2356–65.
212. Itzhaki I, Maizels L, Huber I, et al. Modeling of catecholaminergic polymorphic ventricular tachycardia with patient-specific human-induced pluripotent stem cells. J Am Coll Cardiol 2012;60:990–1000.
213. Gnecchi M, Schwartz PJ. The unstoppable attraction for induced pluripotent stem cells: are they the magic bullet for modeling inherited arrhythmogenic diseases? J Am Coll Cardiol 2012;60:1001–4.
214. Xu Q, Seeger FH, Castillo J, et al. Micro-RNA-34a contributes to the impaired function of bone marrow-derived mononuclear cells from patients with cardiovascular disease. J Am Coll Cardiol 2012;59:2107–17.
215. Wang TY, Angiolillo DJ, Cushman M, et al. Platelet biology and response to antiplatelet therapy in women: implications for the development and use of antiplatelet pharmacotherapies for cardiovascular disease. J Am Coll Cardiol 2012;59:891–900.
216. Voora D, Ginsburg GS. Clinical application of cardiovascular pharmacogenetics. J Am Coll Cardiol 2012;60:9–20.
217. Li TS, Cheng K, Malliaras K, et al. Direct comparison of different stem cell types and subpopulations reveals superior paracrine potency and myocardial repair efficacy with cardiosphere-derived cells. J Am Coll Cardiol 2012;59:942–53.
218. Mohsin S, Khan M, Toko H, et al. Human cardiac progenitor cells engineered with pim-I kinase enhance myocardial repair. J Am Coll Cardiol 2012;60:1278–87.
219. Bishopric NH. A longer, better ride with engineered stem cells. J Am Coll Cardiol 2012;60:1288–90.
220. Roberts R, Stewart AF. Genes and coronary artery disease: where are we? J Am Coll Cardiol 2012;60:1715–21.
221. Feinstein, JA, Benson DW, Dubin AM, Cet al. Hypoplastic left heart syndrome: current considerations and expectations. J Am Coll Cardiol 2012;59:S1–42.
222. Pahl E, Sleeper LA, Canter CE, et al., for the PCMR (Pediatric Cardiomyopathy Registry) Investigators. Incidence of and risk factors for sudden cardiac death in children with dilated cardiomyopathy: a report from the Pediatric Cardiomyopathy Registry. J Am Coll Cardiol 2012;59:607–15.
223. D'Udekem Y, Xu MY, Galati JC, et al. Predictors of survival after single-ventricle palliation: the impact of right ventricular dominance. J Am Coll Cardiol 2012;59:1178–85.
224. Backer CL. The functionally univentricular heart: which is better—right or left ventricle. J Am Coll Cardiol 2012;59:1186–7.
225. Chubb H, Pesonen E, Sivasubramanian S, et al. Long-term outcome following catheter valvotomy for pulmonary atresia with intact ventricular septum. J Am Coll Cardiol 2012;59:1468–76.
226. Attenhofer Jost CH, Connolly HM, Scott CG, Burkhart HM, Warnes CA, Dearani JA. Outcome of cardiac surgery in patients 50 years of age or older with Ebstein anomaly: survival and functional improvement. J Am Coll Cardiol 2012;59:2101–6.
227. Emani SM, McElhinney DB, Tworetzky W, et al. Staged left ventricular recruitment following single ventricle palliation in patients with borderline left heart hypoplasia. J Am Coll Cardiol 2012;60:1966–74.
228. Bautista-Hernandez V, Myers PO, Loyola H, et al. Atrioventricular valve annular remodeling with a bioabsorbable ring in young children. J Am Coll Cardiol 2012;60:2256–8.
229. Cappato R, Castelvecchio S, Ricci C, et al. Clinical efficacy of ivabradine in patients with inappropriate sinus tachycardia: a prospective, randomized, placebo-controlled, double-blind, crossover evaluation. J Am Coll Cardiol 2012;60:1323–9.
230. Scheinman MM, Vedantham V. Ivabradine: a ray of hope for inappropriate sinus tachycardia. J Am Coll Cardiol 2012;60:1330–2.
231. Benetos A, Gautier S, Labat C, et al.Mortality and cardiovascular events are best predicted by low central/peripheral pulse pressure amplification but not by high blood pressure levels in elderly nursing home subjects: the PARTAGE (Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population) study. J Am Coll Cardiol 2012;60:1503–11.
232. Krishnan RM, Adar SD, Szpiro AA, et al. Vascular responses to long- and short-term exposure to fine particulate matter: the MESA Air (Multi-Ethnic Study of Atherosclerosis and Air Pollution). J Am Coll Cardiol 2012;60:2158–66.
233. Brook RD, Rajagopalan S. Chronic air pollution exposure and endothelial dysfunction: what you can't see—can harm you. J Am Coll Cardiol 2012;60:2167–9.
234. Antoniades C, Demosthenous M, Reilly S, et al. Myocardial redox state predicts in-hospital clinical outcome after cardiac surgery effects

of short-term pre-operative statin treatment. J Am Coll Cardiol 2012;59:60–70.
235. Laufs U, Adam O. Acute effects of statins. J Am Coll Cardiol 2012;59:71–3.
236. Willoughby SR, Rajendran S, Chan WD, et al. Ramapril sensitizes platelets to nitric oxide: implications for therapy in high risk patients. J Am Coll Cardiol 2012;60:887–94.
237. Angiolillo DJ, Capodanno D. Targeting platelet nitric oxide resistance with ramipril: unraveling mechanisms of atherothrombotic risk reduction with angiotensin-converting enzyme inhibitors. J Am Coll Cardiol 2012;60:895–7.
238. Lee WW, Marinelli B, van der Laan AM, et al. PET/MRI of inflammation in myocardial infarction. J Am Coll Cardiol 2012;59:153–63.
239. Frantz S, Hofmann U. Monocytes on the scar's edge. J Am Coll Cardiol 2012;59:164–5.
240. Schwartz BG, Levine LA, Comstock G, Stecher VJ, Kloner RA. Cardiac uses of phosphodiesterase-5 inhibitors. J Am Coll Cardiol 2012;59:9–15.
241. Kukreja RC, Salloum FN, Das A. Cyclic guanosine monophosphate signaling and phosphodiesterase-5 inhibitors in cardioprotection. J Am Coll Cardiol 2012;59:1921–7.
242. Molina CE, Leroy J, Richter W, et al. Cyclic adenosine monophosphate phosphodiesterase type 4 protects against atrial arrhythmias. J Am Coll Cardiol 2012;59:2182–90.
243. Van Wagoner DR, Lindsay BD. Phosphodiesterase-4 activity: a critical modulator of atrial contractility and arrhythmogenesis. J Am Coll Cardiol 2012;59:2191–2.
244. Matsubara J, Sugiyama S, Sugamura K, et al. A dipeptidyl peptidase-4 inhibitor, des-fluoro-sitagliptin, improves endothelial function and reduces atherosclerotic lesion formation in apolipoprotein E-deficient mice. J Am Coll Cardiol 2012;59:265–76.
245. Murohara T. Dipeptidyl peptidase-4 inhibitor: another player for cardiovascular protection. J Am Coll Cardiol 2012;59:277–9.
246. Marzilli M, Merz CN, Boden WE, et al. Obstructive coronary atherosclerosis and ischemic heart disease: an elusive link! J Am Coll Cardiol 2012;60:951–6.
247. Patel M, Dunford JV, Aguilar S, et al. Pre-hospital electrocardiography by emergency medical ppersonnel: effects on scene and transport times for chest pain and ST-segment elevation myocardial infarction patients. J Am Coll Cardiol 2012;60:806–11.
248. Hannan EL, Cozzens K, Samadashvili Z, et al. Appropriateness of coronary revascularization for patients without acute coronary syndromes. J Am Coll Cardiol 2012;59:1870–6.
249. Tsimikas S, Willeit P, Willeit J, et al. Oxidation-specific biomarkers, prospective 15-year cardiovascular and stroke outcomes and net reclassification of cardiovascular events. J Am Coll Cardiol 2012;60:2218–29.
250. Clavel MA, Dumesnil JG, Capoulade R, Mathieu P, Senechal M, Pibarot P. Outcome of patients with aortic stenosis, small valve area, and low-flow, low-gradient despite preserved left ventricular ejection fraction. J Am Coll Cardiol 2012;60:1259–67.
251. Baumgartner H. Low-flow, low-gradient aortic stenosis with preserved ejection fraction. J Am Coll Cardiol 2012;60:1268–70.
252. Capoulade R, CLavel MA, Dumesnil JG, et al. Impact of metabolic syndrome on progression of aortic stenosis. J Am Coll Cardiol 2012;60:216–23.
253. Aksoy O, Cam A, Goel SS, et al. Do bisphosphonates slow the progression of aortic stenosis? J Am Coll Cardiol 2012;59:1452–9.
254. Lancellotti P, Magne J, Donal E, et al. Clinical outcome in asymptomatic severe aortic stenosis. J Am Coll Cardiol 2012;59:235–43.
255. Flachskampf FA, Kavianipour M. Varying hemodynamics and differences in prognosis in patients with asymptomatic severe aortic stenosis and preserved ejection fraction. J Am Coll Cardiol 2012;59:244–245.
256. Henkel DM, Malouf J, Connolly HA, et al. Asymptomatic left ventricular systolic dysfunction in patients with severe aortic stenosis: characteristics and outcomes. J Am Coll Cardiol 2012;60:2325–9.
257. Brennan JM, Edwards FH, Zhao Y, et al. Early anticoagulation of bioprosthetic aortic valves in older patients. J Am Coll Cardiol 2012;60:971–7.
258. Whitlock RP, Eikelboom JW. Prevention of thromboembolic events after bioprosthetic aortic valve replacement. J Am Coll Cardiol 2012;60:978–80.
259. Whitlow PL, Feldman T, Pedersen WR, et al. Acute and 12 month results with catheter-based mitral valve leaflet repair. J Am Coll Cardiol 2012;59:130–9.
260. Turi ZG, Rosenbloom M.An option for the high-comorbidity patient with mitral regurgitation. J Am Coll Cardiol 2012;59:140–2.
261. Arabkhani B, Heuvelman HJ, Bogers AJJC, Mokhles M, Roos-Hesselink JW, Takkenberg JJM. Does pregnancy influence the durability of human aortic valve substitutes? J Am Coll Cardiol 2012;60:1991–2.